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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
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Safety of Anti-TNF Therapies in Immune-Mediated Inflammatory Diseases: Focus on Infections and Malignancy

Rui Miguel Pedrosa Pereira

DISSERTAÇÃO DE MESTRADO INTEGRADO EM **MEDICINA**

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Safety of Anti-TNF Therapies in Immune-Mediated Inflammatory Diseases: Focus on Infections and Malignancy

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NOTA INTRODUTÓRIA

A presente dissertação de mestrado, apresentada na modalidade "Artigo de Investigação", resultou de um projeto de investigação desenvolvido no âmbito da unidade curricular "Disciplina de Iniciação à Investigação Clínica" (DIIC) do Mestrado Integrado em Medicina do Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

A proposta de projeto foi elaborada no ano letivo de 2014/2015, tendo sido submetida e aprovada pela Comissão de Ética e pelo Gabinete Coordenador da Investigação do Departamento de Ensino, Formação e Investigação, e autorizada pelo Conselho de Administração do Centro Hospitalar do Porto [2015.120(107-DEFI/100-CES)].

O projeto foi realizado no Serviço de Dermatologia, no ano letivo 2015/2016, sob a orientação do Professor Doutor Tiago Torres, com a supervisão da Professora Doutora Margarida Lima, regente da DIIC.

Do projeto resultaram: um artigo científico de revisão publicado na revista *Drug Development Research*, dois artigos científicos originais para publicação e um trabalho apresentado, na forma de *poster,* nas XXVIII Jornadas de Terapêutica.

A dissertação encontra-se estruturada em quatro partes:

1. Artigo de revisão "***Safety of Anti-TNF Therapies in Immune-Mediated Inflammatory Diseases: Focus on Infections and Malignancy***" publicado na revista *Drug Development Research;*

2. Artigo original "***Assessment of hepatitis B reactivation in patients treated with anti-TNF therapy with past HBV exposure***" submetido para publicação na revista *Internal Medicine Journal*;

3. Artigo original "***Infection and malignancy risk in patients treated with TNF inhibitors for immune-mediated inflammatory diseases***" para publicação em revista científica da área;

4. Trabalho apresentado na forma de *poster* nas XXVIII Jornadas de Terapêutica.

Como apêndice é apresentada a proposta do projeto de investigação, tal como foi aprovada, e como anexos, os respetivos documentos de submissão e autorização.

INTRODUÇÃO

O conceito de doenças inflamatórias imunomediadas engloba um vasto leque de patologias crónicas, altamente incapacitantes, que, embora não estejam clinicamente relacionadas, partilham uma desregulação do sistema imunológico na qual a inflamação tem um papel central. Estima-se que, coletivamente, afetem até 7% da população ocidental. O tratamento destas doenças incide sobre o controlo da inflamação e prevenção do dano tecidular com o objetivo de remissão a longo prazo, melhorando a qualidade de vida. Os inibidores do fator de necrose tumoral (anti-TNF) estão aprovados no tratamento de várias doenças inflamatórias imunomediadas incluindo a doença inflamatória intestinal, artrite reumatóide, psoríase e artrite psoriática, espondilite anquilosante e artrite idiopática juvenil, modificando o prognóstico das mesmas. Atualmente existem 5 agentes anti-TNF (infliximab, adalimumab, etanercept, certolizumab pegol e golimumab) que possuem indicações terapêuticas diferentes.

Apesar de estes agentes terem mais de uma década de uso clínico em diversas patologias, existem ainda resultados inconsistentes no que toca ao perfil de segurança. Em relação aos eventos adversos infeciosos existem, de facto, estudos que mostram um aumento na taxa de infeção grave, enquanto outros negam esse achado. O fator de necrose tumoral possui um papel chave na formação de granulomas e, como tal, existe um risco reconhecido de reativação de tuberculose latente. Este ponto é particularmente importante visto que esta infeção tem uma relevância central na realidade portuguesa. Os estudos mais recentes não associam os anti-TNF a um risco aumentado de tumores sólidos ou hematológicos com a exceção de neoplasias cutâneas (incluindo melanoma).

Tanto quanto apuramos, não existem estudos a comparar o risco destes efeitos adversos nas diferentes doenças inflamatórias imunomediadas. O objetivo deste estudo retrospetivo é descrever a experiência de um hospital terciário relativamente aos efeitos adversos infeciosos e malignos durante terapêuticas anti-TNF. Tanto quanto sabemos este é o primeiro estudo do género em Portugal, principalmente com uma amostra abrangente de todas as áreas clínicas que utilizam agentes anti-TNF e com um período observacional tão alargado.

ÍNDICE

PARTE 1: *SAFETY OF ANTI-TNF THERAPIES IN IMMUNE-MEDIATED INFLAMMATORY DISEASES: FOCUS ON INFECTIONS AND MALIGNANCY*

DRUG DEVELOPMENT RESEARCH 76 : 419–427 (2015)

DDR

Review Article

Safety of Anti-TNF Therapies in Immune-Mediated Inflammatory Diseases: Focus on Infections and Malignancy

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Strategy, Management and Health Policy				
Enabling Technology, Genomics, Proteomics	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT The efficacy of anti-TNF agents in the treatment of multiple immune-mediated inflammatory diseases (IMIDs) has increased their daily use. However, concerns remain regarding their long-term safety profile. Using a literature-based review of the infectious and malignant complications of anti-TNF biologics in IMIDs including psoriasis, Rheumatoid Arthritis, and inflammatory bowel disease, this review presents current evidence relative to the safety of anti-TNF agents in the context infections and malignancy in adults with IMIDs. Treatment with anti-TNF biologics is an effective treatment option with known risks that can be mitigated by appreciating the safety aspects and via a thorough screening and continuous monitoring of the patient. Drug Dev Res 76 : 419–427, 2015.

Key words: immune-mediated inflammatory diseases; psoriasis; rheumatoid arthritis; inflammatory bowel disease; safety; infection; malignancy; anti-TNFa therapies

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) are defined as a group of chronic and highly incapacitating conditions that while not clinically related share an immune dysregulation caused or accompanied by acute or chronic inflammation [Williams and Meyers, 2002; Kuek et al., 2007]. They are estimated to affect 5–7% of the population in Western countries [Beyaert et al., 2013] and their treatment focuses on the rapid control of inflammation and prevention of tissue damage, with the goal of long-term remission of the disease, thus improving quality of life and preventing damage. The primary therapeutic assets available are corticosteroids, classic and biological Disease-Modifying Antirheumatic Drugs (DMARDs), especially those targeting tumor necrosis factor (TNF) [Beyaert et al., 2013].

Anti-TNF therapies were introduced into clinical practice in 1998 for the treatment of inflammatory bowel diseases (IBDs), and Rheumatoid Arthritis (RA) and have significantly changed the treatment and outcome of a number of inflammatory diseases [Geiler et al., 2011]. While some concerns regarding the safety and efficacy of these agents remain, data concerning this topic is better defined after more than a decade of treatment for diverse diseases. Even

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so, different studies have had inconsistent results concerning the safety profile. Some reports state that there is no significant increase in serious infections [Peyrin–Biroulet et al., 2008; Leombruno and Keystone, 2009; Fouque-Aubert et al., 2010], while others indicate an increase in the overall serious infection rate [Komano et al., 2011; Galloway et al., 2013]. Additionally, patients with chronic inflammatory diseases have a higher risk of infection and malignancy for several disease-related reasons despite treatment [Doran et al., 2002; Beyaert et al., 2013; Johnston et al., 2013]. The increased risk of developing tuberculosis (TB) has been of special concern since TNF has an important biological role in the formation of granuloma and containment of disease [Senaldi et al., 1996]. Regarding malignancy, earlier studies reported increased risk of lymphoma and malignancies overall [Wolfe and Michaud, 2004; Bongartz et al., 2006]. However more recent studies and registry databases have not associated anti-TNF biologics with an increased risk in solid or hematologic malignancies [Keystone, 2003; Askling, 2005a, 2005b; Wolfe and Michaud, 2007b; Peyrin–Biroulet et al., 2008; Leombruno and Keystone, 2009; Saad et al., 2010; Dommasch et al., 2011; Moulis et al., 2012;] with the exception of melanoma and non-melanoma skin cancer (NMSC) [Wolfe and Michaud, 2007a; Askling et al., 2011].

The aim of the present review is to collect information regarding anti-TNF therapies focusing on infections and malignancy in patients treated in the following diseases: Psoriasis (Ps) and Psoriatic Arthritis (PsA), RA, Ankylosing Spondylitis (AS), Juvenile Idiopathic Arthritis (JIA), and IBDs including Crohn's Disease (CD) and Ulcerative Colitis (UC).

MATERIALS AND METHODS

Articles from January 2010 to December 2014 were searched in the PubMed database, using the following keywords: safety, adverse event, IMIDs, anti-TNF, anti-TNF, Ps, IBD, RA, AS, JIA, CD, UC, infection, and malignancy. Additional relevant references in these articles were also included in the review. The search results were then supplemented by including other documents suggested by the experience of the authors.

TNF-α Mechanism of Action

TNF-α is a proinflammatory cytokine involved in an intricate inflammatory network that plays a role not only in innate but also in adaptive immunity. TNF-α modulates monocyte differentiation, induces the production of an assortment of chemokines and adhesion molecules. It can stimulate T-cell proliferation and also promote T-cell apoptosis and the termination of immune response. At low levels, TNF-α has beneficial effects in the tissue, e.g., an increase in host defense mechanisms against infections; conversely high concentrations may lead to excess inflammation and organ injury [Bachmann et al., 2010]. The decrease in apoptosis at inflammation sites is hypothesized to be the cause of chronic inflammation verified in diseases such as RA and CD [Sands, 2004; Tak, 2005].

TNF-α dysregulation plays a central role in numerous pathological conditions including the IMIDs. Although the precise etiology for each IMID is not entirely known there are some basic concepts regarding the pivotal role of TNF-α. For instance, the increased expression of adhesion molecules in Ps, promoting the influx of leukocytes to the inflammation site, is central in the genesis of the inflammatory process in the psoriatic epidermis [Victor et al., 2003]. TNF-α also leads to keratinocyte hyperproliferation and increases VEGF expression, promoting angiogenesis, which performs a central role in changing the morphology of blood vessels observed in psoriatic skin [Silva et al., 2010]. TNF-α is thought to be linked with the upregulation of hepcidin and PGE_2, osteoclast activation (bone resorption) and chondrocyte activation (metalloproteinase production, cartilage destruction) observed in RA [Silva et al., 2010]. A key role in IBD is demonstrated by the elevated TNF-α in the intestinal mucosa, feces, and serum of such patients. Furthermore, CD exacerbated Th-1 inflammatory response of the gut appears to result from the TNF-α excess [Silva et al., 2010].

Anti-TNF Structure and Mechanism of Action

Five TNF-α inhibitors are in clinical use: infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab. While differing in structure, pharmacokinetics, mechanism(s) of action and indications these all block the biological effects of TNF-α with the efficacy and safety profiles being considered as a class effect. Nevertheless, some differences may exist among the five agents.

Infliximab (Remicade®) is a chimeric human/murine IgG1 monoclonal antibody (mAb) directed against TNF-α [Murdaca et al., 2012]. Infliximab is highly effective in the treatment of chronic inflammatory diseases including CD, UC, RA, AS, PsA, and plaque psoriasis [Janssen Biotech, Inc., 2013a]. *Adalimumab* (Humira®) is a fully recombinant human IgG1 anti-TNF specific mAb [Murdaca et al., 2012]

and it is indicated in the treatment of RA, JIA, PsA, AS, CD, UC, and plaque psoriasis [AbbVie Inc., 2014].

Golimumab (Simponi®) is a human γ-1 immunoglobulin-κ anti-TNF monoclonal antibody [Murdaca et al., 2012]. It is currently indicated for adult patients with RA, PsA, AS, and UC [Janssen Biotech, Inc., 2013b].

Etanercept (Enbrel®) is not a monoclonal antibody, but a fusion protein that acts as a "decoy receptor" for TNF-α competing to inhibit the binding of TNF-α to its cell surface receptor [Murdaca et al., 2012]. Etanercept is approved for the treatment of RA, polyarticular JIA, PsA, AS, and Ps [Immunex Corporation, 2013].

Certolizumab pegol (Cimzia®) differs from the other anti-TNF by its structure, being composed of the Fab antigen-binding domain of a humanized monoclonal anti-TNF antibody combined with polyethylene glycol that increases its half-life [Murdaca et al., 2012]. It is currently approved for CD, RA, PsA, and AS [UCB, 2013].

Safety

Anti-TNF therapeutics are usually well tolerated, however, potential adverse events that have been highlighted include infusion and injection-site reactions, autoimmunity, demyelinating disease, and other neurological symptoms, heart failure, infections with special regard to TB and malignancy [Murdaca et al., 2012; Chimenti et al., 2014; McLean and Cross, 2014;]. Patients under high-dose regimens of TNF-α therapy have not shown more frequent adverse effects than patients receiving standard doses. However, since dose escalation is considered an off-label regimen thus, the safety data are restricted [Brezinski and Armstrong, 2012].

Infections

Although patients with IMIDs are usually at increased risk of infection due to baseline disease activity or the disease pathophysiology itself [Germano et al., 2014], the risk of infections, especially TB, reflect key safety concerns regarding the use anti-TNF biologics. The most commonly reported infections are those of the respiratory tract that are consistent through several studies in patients treated with anti-TNF agents [Grijalva et al., 2010 Grijalva et al., 2011; Germano et al., 2014]. After those, gastrointestinal, urogenital, and cutaneous/soft tissue are the most reported infections [Germano et al., 2014].

Infections that require antimicrobial therapy and/or hospitalization are often reported as serious. Some studies, albeit not all, report an increase in serious infection risk in patients undergoing anti-TNF therapeutics. Monoclonal antibody clinical trials (infliximab and adalimumab) reported a twofold increase in serious infection risk [Bongartz et al., 2006]. An unrelated meta-analysis evaluating serious infection risk within RA trials of etanercept, infliximab, and adalimumab found no statistically increased risk (RR 1.08; 95% CI: 0.81–1.43) in those treated with anti-TNF therapy versus placebo, but did find a significant twofold increase in risk for those studies using higher-dose infliximab or adalimumab [Leombruno and Keystone, 2009]. A Cochrane review of anti-TNF therapies across disease indications found infliximab (OR 1.41; 95% CI: 0.75–2.62) and certolizumab (OR 4.75; 95% CI: 1.52–18.5) to have the highest OR of serious infection compared with control treatment [Singh et al., 2011]. A large retrospective study of veterans under anti-TNF therapies, reported that 7% of these patients had at least one admission for a serious infection [Lane et al., 2011]. The higher risk of hospitalization was associated with the use of infliximab relative to etanercept and adalimumab [Grijalva et al., 2011]. Conversely, in a large cohort of patients with IMIDs, TNF-α antagonist treatment was not associated with an increased risk of hospitalizations for serious infections, compared with non-biologic treatment [Grijalva et al., 2011]. Exposure to more than one anti-TNF agent during therapy may also be related with a twofold risk of developing a serious infection [Alawneh et al., 2014].

Infections in the surgical setting are also a concern regarding anti-TNF therapies. The information regarding postoperative setting with the use of infliximab in UC patients demonstrated no increase in overall complication rates [Yang et al., 2012], but on the other hand, CD complications were increased. Both local and non-local infections occurred more commonly while on infliximab and a trend was noted regarding overall and non-infectious complications [Kopylov et al., 2012]. Another study also demonstrated that preoperative anti-TNF exposure was a predictor of both overall infections (OR: 2.4; 95% CI: 1.2–5.0) and surgical site (OR: 2.0; 95% CI: 1.0–3.8) complications [Syed et al., 2013]. The findings regarding the increased risk in IBD patients were reinforced in a meta-analysis study [Narula et al., 2013]. the Data available regarding Pas patients treated with anti-TNF, appears to indicate that there is no increase in postoperative infections [Fabiano et al., 2014 Bakkour et al., 2015].

Combination therapy whether with corticosteroids or immunomodulators is frequently encountered in patients undergoing anti-TNF biologics due to the severity of the disease. A study involving RA,

AS, and PsA patients found that combined therapy, especially with corticosteroids, significantly increased infection risk [Germano et al., 2014]. Overall, TNF inhibitors, both as monotherapy (OR 2.17; CI: 1.32-3.57) or in association with immunomodulators (OR 3.11; CI: 1.77-5.46), systemic corticosteroids (OR 1.92; CI: 1.10-3.34) or both (OR 3.64; CI: 1.96-6.74), significantly increased the overall odds of infection in IBD patients [Deepak et al., 2013]. The likelihood of infectious complications is substantial and is markedly elevated in case of combined immunosuppression [Fellermann, 2013].

Viruses, mainly members of the herpes virus family, are the predominant infectious agents recorded in pediatric and adolescent JIA patients [Toussi et al., 2013]. Zoster frequently occurs in RA patients, however data regarding the risk of anti-TNF therapy are conflicting [Winthrop and Furst, 2010]. No significant differences were found in RA patients treated with anti-TNF between themselves or versus DMARDs [Winthrop et al., 2013b]. A meta-analysis study revealed an increased risk of Zoster in patients receiving anti-TNF therapies. However, the absolute risk was very low, raising the issue of prophylactic treatment regarding Zoster infection [Che et al., 2014]. For Hepatitis B infection, anti-TNF treatment is a relatively safe regiment if appropriate precautions are taken. Viral reactivation occurs in patients treated with anti-TNF agents [Pérez-Alvarez et al., 2011; Urata et al., 2011]. HBV reactivation is related to the serological status prior to anti-TNF therapy with a higher reactivation in HBsAg positive patients compared to those that are anti-HBc positive [Pérez-Alvarez et al., 2011]. Screening for chronic HBV infection with hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) is recommended in all patients prior to initiating anti-TNF treatment. Nonetheless, anti-TNF appears as a safe option in patients with chronic HBV infection when combined with antiviral therapy in HBsAg positive patients as well as without any prophylaxis in anti-HBc positive patients but with close monitoring [Vassilopoulos et al., 2010; Ballanti et al., 2014].

Anti-TNF therapy has been associated with increased risk of serious and opportunistic infections in patients with IBD [Colombel et al., 2004; Toruner et al., 2008; Marehbian et al., 2009]. In RA cohorts, infliximab increased the risk for opportunistic infections, compared to etanercept and methotrexate [Salmon-Ceron et al., 2011; Baddley et al., 2014]. Concomitant immunosuppression, especially with steroids, represents an additional risk factor for opportunistic infections among patients receiving anti-TNF therapies [Salmon-Ceron et al., 2011; Baddley et al., 2014]. The risk of endemic mycoses (histoplasmosis, coccidoidomycosis, and blastomycosis) and TB varies according to geography and baseline risk [Winthrop, 2012]. Thus the overall risk of opportunistic infections should be considered before inititaing therapy [Girgis et al., 2007]. TNF biologicals increased the risk for non-TB mycobacterial diseases compared to both RA patients undergoing a different treatment and to the general population [Winthrop et al., 2013a]. Atypical manifestations of infectious such as cytomegalovirus infection, histoplasmosis, *Pneumocystis jirovecii* pneumonia, and aspergillosis have been reported [Fellermann, 2013]. A recent meta-analysis of 22 randomized controlled trials in IBD found that the relative risk of developing an opportunistic infection was significantly higher in patients receiving anti-TNF therapy (RR: 2.1; 95% CI: 1.1–3.9) [Ford and Peyrin-Biroulet, 2013].

TB is one of the major concerns in patients exposed to anti-TNF agents as they are at increased risk of developing or reactivating TB in cases of latent infection [Marehbian et al., 2009]. Anti-TNF therapies have an increased risk of developing TB compared to the general population [Mariette et al., 2011; Lee et al., 2013; Winthrop et al., 2013a]. Although TB risk has been recognized as a class effect, it is up to fourfold more common in adalimumab and infliximab-treated patients (monoclonal antibodies) relative to etanercept-treated patients (soluble TNF receptor) [Tubach et al., 2009; Dixon et al., 2010; Winthrop et al., 2013a]. TB in anti-TNF therapies setting is more often disseminated, atypical, extrapulmonary, and life threatening. Extrapulmonary TB was constituted more than 50% of cases of TB in this setting [Keane et al., 2001; Dixon et al., 2010; Jauregui-Amezaga et al., 2013]. Moreover, extrapulmonary TB has been reported in patients receiving anti-TNF therapy despite negative screening with a tuberculin skin test (TST) [Alawneh et al., 2014]. The introduction of latent TB infection screening prior to initiation of therapy precipitated a reduction of the incidence of TB, bringing it close to the levels of the background population [Carmona et al., 2005]. On the other hand, there are still TB cases being reported despite appropriate measures [Jauregui-Amezaga et al., 2013]. Due to this acknowledged risk, prescribers are advised to evaluate patients for TB risk factors and test for LTB prior to beginning therapy as well as periodically during therapy [Solovic et al., 2010].

Adherence to certain guidelines can ensure a safer anti-TNF treatment course [Nordgaard-Lassen et al., 2012]. Accepted good practices include screening for active or latent TB, vaccination against HBV, varicella zoster virus, influenza (annually), and human

papilloma virus in young females [Neuman and Nanau, 2014].

Malignancy

IMIDs have been associated with an increased risk of malignancy due to the protumorigenic effects of inflammation [Beyaert et al., 2013]. Patients with RA are at an approximately twofold increased risk for lymphoma and leukemia, as well as an increased risk for respiratory tract cancer and NMSC, but at decreased risk for breast and colorectal cancer (CRC) [Askling, 2005a,b]. A meta-analysis confirmed the increased risk for lung cancer, twofold higher risk for lymphoma and decreased risk for colorectal and breast cancer in RA [Smitten et al., 2008]. Another study reported that the increased lymphoma risk is limited to a subset of RA patients with very severe disease and thus related to the high inflammatory activity, rather than its treatment [Baecklund et al., 2006]. Patients with IBD are at increased risk for gastrointestinal malignancies, including CRC and small bowel cancer [Kappelman et al., 2014]. Various disease subgroups carry increased risk of gastrointestinal malignancy, e.g. those with persistent inflammation, extensive disease, long-standing disease, age at diagnosis, and coexisting primary sclerosing cholangitis [Munkholm, 2003; Kappelman et al., 2014]. Disease duration and grade of inflammation are the main driving forces of dysplasia and CRC development [Munkholm, 2003; Kappelman et al., 2014]. Also the risk of extraintestinal cancer including lymphoproliferative disorders, cholangiocarcinoma, and skin cancer is increased in IBD with concomitant diseases including primary sclerosing cholangitis predispose patients to malignancies like cholangiocarcinoma. Disease factors and degree of immunossupressive medications and duration are important risk factors for the development of lymphoproliferative disorders and skin cancer [Kappelman et al., 2014; Magro et al., 2014].

In Ps, studies from the prebiologics era described an increased risk for lymphoma, NMSC, and cancers linked with alcohol and smoking [Hannuksela-Svahn et al., 2000]. Cancer risk appears to be higher in patients with severe Ps, which raises the question whether the cancer risk perceived across the diverse IMIDs is caused by chronic inflammation or by the systemic treatments used with the increased severity of this diseases [Margolis et al., 2001].

Treatment with anti-TNF agents was not associated with an increased cancer risk compared to placebo in RA patients treated for up to 2 years according to data from 33 placebo-controlled trials. Notwithstanding, these data showed a trend toward an increased risk of NMSC [Moulis et al., 2012]. Additionally, evidence regarding a TNF-α inhibitor association with an increased risk of lymphoma is not convincing. A large longitudinal study evaluated data from 19,562 RA patients with 89,710 person-years of follow-up and no association was found (OR: 1.0; 95% CI: 0.6–1.8) [Wolfe and Michaud, 2007b]. However the question is whether if significant differences are unclear due to the relatively low incidence of these adverse effects [Keystone, 2011]. In IBD patients, particularly those with CD, as previously noted, an increased risk of melanoma was shown in one study (OR: 1.8; 95% CI: 1.1–3.3) [Long et al., 2012] although conflicting information exists [Fellermann, 2013]. There is minimal evidence to support an increased risk of lymphoproliferative disorders and solid tumors in IBD resulting from anti-TNF monotherapy [Hudesman et al., 2013; Biancone et al., 2014]. In Ps, anti-TNF biologics do not appear to increase the risk of lymphoproliferative or solid malignancies in comparison with any other treatment currently available [Kimball et al. 2014]. It is important to point out the difficulty to extrapolate cancer risk in any of the aforementioned studies because of the small number of patients and reduced follow-up. When cancer does develop during anti-TNF therapy, it is advised to interrupt the treatment until the cancer is controlled [Beaugerie, 2011].

CONCLUSIONS

Biologicals and anti-TNF agents in particular have revolutionized treatment of IMIDs. Nonetheless, there are safety concerns related to the immunosuppressant effect of anti-TNF agents that have surfaced through the years of trials, studies, and clinical use that are not negligible. The safety concerns vary from infusion and injection-site reactions to life threatening and therapy ending side effects such as infections and malignancy. The group of diseases for which anti-TNF are used (IMIDs) have an inherent increased risk of complications e.g., infections and malignancy. Furthermore, greater disease severity, often the setting of anti-TNF treatment, is associated with a more intense inflammatory environment that is prone to either one of the complications in study. From the data reviewed, there is an apparent increased risk of infection in patients treated with anti-TNF biologics. As for malignancy, there is insufficient evidence for a direct association nonetheless a frequent limitation of the reviewed studies is the short follow-up that may result in biased results. To avoid such side effects the prescribing physician should be aware of the possible complications of this

therapeutic weapon, the current recommendations on screening and provide adequate follow up to the patient.

DISCLOSURES OF COMMERCIAL INTEREST AND ROLES

Rui Pereira has no conflicts of interest to disclosure. Paula Lago has received honoraria for acting as a consultant and/or as a speaker at events sponsored by AbbVie, MSD, Ferring and OM Pharma. Raquel Faria has participated in clinical trials sponsored by AbbVie, Amgen, Novartis, and Boeringher and has received honoraria for acting as a consultant and/or as a speaker at events sponsored by Menarini and Glaxo-Smith-Klein. Tiago Torres has participated in clinical trials sponsored by AbbVie, Amgen, and Novartis and has received honoraria for acting as a consultant and/or as a speaker at events sponsored by AbbVie, Boehringer Ingelheim, Janssen, Leo-Pharma, MSD, Novartis, and Pfizer.

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PARTE 2: *ASSESSMENT OF HEPATITIS B REACTIVATION IN PATIENTS WITH PAST HBV EXPOSURE TREATED WITH ANTI-TNF THERAPY*

Assessment of hepatitis B reactivation in patients with past HBV exposure treated with anti-TNF therapy

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Abstract

Background: The risk of hepatitis B virus (HBV) reactivation in patients with past exposure to HBV (positive antibodies to hepatitis B core antigen (anti-HBc), negative hepatitis B surface antigen (HBsAg) and HBV-DNA, with or without antibodies to hepatitis B surface antigen (anti-HBs)] treated with anti-tumor necrosis factor (anti-TNFα) agents is uncertain. Aims: The aim of the present study was to evaluate the safety of anti-TNFα therapy in anti-HBc positive/HBsAg negative patients with any indication for this biologic therapy. **Methods:** Anti-HBc positive/HBsAg negative subjects treated for immune-mediated inflammatory diseases (IMIDs) with anti-TNFα (Infliximab, Adalimumab, Etanercept and Golimumab) from January 2000 to December 2014 in a Tertiary Hospital were included. **Results:** From a total of 389 patients that were treated with anti-TNFα, 26 patients had serologic profile compatible with a previous HBV infection. The mean observation time was 43.6 ± 28.7 months. No case of reactivation was detected regardless of anti-HBs positivity (no increase in aminotransferases above normal range, de novo detection of HBV-DNA or HBsAg seroconversion). **Conclusion:** This retrospective study supports the available data regarding the safety of anti-TNFα therapy in patients with HBV past exposure.

Keywords: anti-TNFα, HBV reactivation, past exposure, Immune-mediated inflammatory disease

Introduction

Anti-tumor necrosis factor (anti-TNFα) agents revolutionized the treatment of inflammatory diseases such as psoriasis, spondyloarthropathies, rheumatoid arthritis and inflammatory bowel disease (IBD). However given their immunosuppressive nature, these agents increase susceptibility to new infections and alter the natural course of latent infections such as Hepatitis B virus (HBV) (1-3).

Hepatitis B infection can be classified in different disease stages depending on the interpretation of the analytic and serologic profile of each patient (4). Occult HBV infection is defined as the persistence of viral genome in the liver tissue of individuals serologically negative for hepatitis B surface antigen (HBsAg). Due to the difficulty in identifying HBV-DNA through liver biopsy and the rarity of detectable serum viremia, some consider patients with positive

antibodies to hepatitis B core antigen (anti-HBc), negative HBsAg and HBV-DNA, with or without antibodies to hepatitis B surface antigen (anti-HBs) as potential occult HBV carriers (5).

In patients with positive HBsAg, antiviral prophylaxis is required before biological treatment is initiated (6). In the group of patients with past HBV infection (positive anti-HBc and negative HBsAg), an unknown percentage may carry an occult infection and reactivate upon exposure to the immunosuppressive therapy (7, 8). Studies in subjects with past HBV infection treated with anti-TNFα therapy for inflammatory bowel disease and rheumatic diseases estimated a reactivation rate between 1.7% and 5% of patients (7, 8).

The aim of this retrospective study was to evaluate the rate of reactivation in anti-HBc positive/HBsAg negative patients treated with anti-TNFα agents for psoriasis, rheumatologic diseases and inflammatory bowel diseases.

Methods

Patients treated for Immune-mediated inflammatory diseases (IMIDs) such as psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, rheumatoid arthritis, Crohn's disease and ulcerative colitis with anti-TNFα (Infliximab, Adalimumab, Etanercept and Golimumab) from January 2000 to December 2014, for at least a month, in a Tertiary Hospital were included. Information regarding the patients' hepatitis B screening serology (HBsAg, anti-HBc, anti-HBs) and HBV-DNA (in anti-HBc positive patients) prior to the initiation of immunosuppressive therapy as well as HBsAg seroconversion, HBV-DNA de novo detection and ALT/AST levels during anti-TNF therapy were collected. HBV reactivation was defined on the basis of a titer elevation of 2 to 3 times the upper limit of normal of ALT, in combination with de novo detection of HBV-DNA or an increase over 10-fold of the HBV-DNA relative to the title before the initiation of therapy or HBsAg seroconversion.

Furthermore, the patients clinical and demographic characteristics such as age, gender, disease duration, treatment [anti-TNFα in monotherapy or combined with corticosteroids and/or other immunosuppressant's [methotrexate, azathioprine] and treatment duration were recorded.

Results

From a total of 389 patients that were treated with anti-TNFα biologics from January 2000 to December 2014, 292 (75%) were screened before the initiation of treatment while the remaining 97 (25%) had no recorded pre-treatment screening. In patients in which a pre-treatment screening was performed, 237 (81%) had no positive marker, 28 (10%) were only anti-HBs positive (previous immunization), 26 (9%) patients were anti-HBc positive/HBsAg negative and one patient presented with a serologic profile compatible with chronic hepatitis B.

The mean observation time was 43.6 ± 28.7 months.

Demographic as well as clinical baseline parameters of the subjects are reported in Table 1. Among the 26 anti-HBc positive/HBsAg negative patients, 19

(73.1%) were anti-HBs positive in the pre-treatment screening. During the observational period 3 (11.5%) other patients were found to be anti-HBs positive. HBV-DNA levels were only available in 7 out of 26 (26.9%) patients nonetheless they were, when present, undetectable at enrolment. Additionally, during follow up, HBV-DNA levels were measured in 7 additional patients amounting to 14/26 (53.8%) patients with undetectable HBV-DNA levels. At baseline, the values of aminotransferases (AST and ALT) were within the normal range and values above normal range were not observed during the observational period. At the end of the observational period, no case of reactivation was observed in anti-HBc positive/HBsAg negative patients regardless of anti-HBs positivity.

Table 1 - Baseline characteristics of 26 anti-HBc positive/ HBsAg negative patients

Patients	26 (100%)
Female gender N (%)	10 (38.5)
Age in years, mean ± SD	52,65 ± 14.125
Disease duration in years, mean ± SD	19,16 ± 11.926
CD N (%)	9 (34.6)
RA N (%)	4 (15.4)
AS N (%)	4 (15.4)
Ps+PsA N (%)	6 (23.1)
Ps N (%)	3 (11.5)
Anti-TNFα N (%)	26 (100)
Etanercept N (%)	12 (46.2)
Adalimumab N (%)	8 (30.8)
Infliximab N (%)	6 (23.1)
Switch N (%)	7 (26.9)
Combined Therapy N (%)	13 (50)
MTX N (%)	7 (26.9)
AZA N (%)	4 (15.4)
CsA N (%)	1 (3.8)
CS N (%)	4 (15.4)

CD **Chron's disease**; RA **rheumatoid arthritis**; AS **ankylosing spondylitis**; Ps **psoriasis**; PsA **psoriatic arthritis**; MTX **methotrexate**; AZA **azathioprine**; CsA **cyclosporine A**; CS **corticosteroids**

Discussion

HBV reactivation is a well-known risk in HBsAg positive patients treated with a wide variety of immunosuppressive therapies such those used in hematopoietic stem cell transplantation, corticosteroids, anthracyclines and rituximab in addition to anti-TNFα agents. Patients with past HBV infection can arbor an occult infection, and thus, be susceptible to reactivation when exposed to immunosuppression. Depending on the inflammatory pathways they suppress or modulate, immunosuppressive agents of different classes have shown to be responsible for different absolute risks of latent infection reactivation (9). It is largely accepted that anti-TNFα agents may lead to HBV reactivation in this subset of patients, although in a recent meta-analysis involving patients with rheumatologic and dermatologic conditions, reactivation rates were found to be much lower when compared to HBsAg positive patients. (10).

The prevalence of anti-HBc positive/HBsAg negative patients was 9% in the present study. Previous studies in patients with chronic inflammatory arthropathies treated with anti-TNFα identified a 9- 2% prevalence of anti-HBc positive/ HBsAg negative patients (2, 11). Some studies that took place in higher prevalence areas detected even higher rates.(12, 13). In the present study, the biological treatment caused no apparent reactivation of hepatitis B virus. Most studies regarding this subject were undertaken in patients treated with anti-TNFα for rheumatoid arthritis and/or spondyloarthropathies and, in concordance with the present study, reported no reactivations (2, 11, 14-16). Likewise a retrospective study involving 13

patients with Psoriasis showed no reactivations (1). To the authors' knowledge there are no studies focusing on anti-HBc positive/HBsAg negative patients treated anti-TNF therapy for IBD. Pérez-Alvarez et al. in a systematic review analyzed 168 anti-HBc positive/HBsAg negative patients in studies/ case reports of patients with RA, spondyloarthropathies, psoriasis as well as IBD. HBV was reactivated in 9 out of those 168 patients (5,4%) (7). A meta-analysis by Lee et al. covered 9 clinical studies summing up to 468 anti-HBc positive/ HBsAg negative patients treated with anti-TNFα for rheumatologic diseases. In 5 of the 9 clinical studies no HBV reactivation was detected. HBV reactivation was observed in 8/468 patients (1.7%) with a percentage of HBV reactivation ranging from 0 to 8.3% (8). Given the reported risk of reactivation in previous studies using anti-TNFα which can lead to serious life-threatening complications through disease flare that may lead to hepatic insufficiency, close monitoring of this patient group should be advised.

In this study, all patients that had HBV DNA measured during screening, maintained their levels below detection threshold during follow up. The above mentioned studies had similar results concerning the lack of HBV-DNA positivity at baseline (2, 11, 14-16). There has been at least one retrospective study that found detectable baseline viral loads in this subset of patients. Lan et al. identified measureable HBV-DNA levels in 4/12 (33.3%) anti-HBc positive/HBsAg negative patients in a study of rheumatoid arthritis patients in Southeast Asia (17).

Although we registered no reactivation, there are studies that appear to indicate that the title of anti-HBs influences the risk of reactivation of hepatitis B virus. Kato et al. found that the 6 anti-HBc positive/HBsAg negative patients who experienced HBV reactivation had significantly lower baseline titers of anti-HBs (18). In the present study, 73.1% patients were anti-HBs positive in the pre-treatment screening and, by the end of the observational period, that number increased to 84.6%. The significance of this finding requires further studies.

The present study presented some limitations, due to its retrospective nature and the relatively small patient sample. Patients with diverse IMIDs (Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis and psoriatic arthritis) that were treated with anti-TNFα biologics were included. Thus the analysis was not limited to a specific subgroup of patients therefore increasing the heterogeneity. Although there is a screening protocol in the authors' hospital, some anti-HBc positive/ HBsAg negative patients still have missing HBV-DNA levels and a deficiency in serologic follow up during anti-TNFα treatment.

European Association for the Study of the Liver (EASL) guidelines state that candidates for chemotherapy and immunosuppressive therapy who are HBsAg positive should be tested for HBV-DNA levels and receive pre-emptive nucleotide analogues during therapy (regardless of HBV-DNA levels) and for 12 months after cessation of therapy (level of evidence A1). Furthermore, it is reported that most experience with pre-emptive treatment was with lamivudine. On the other hand, it is recommended that anti-HBc positive/ HBsAg negative patients with undetectable serum HBV-DNA, regardless of anti-HBs status, who receive chemotherapy and/or

immunosuppression should be followed carefully by means of ALT and HBV-DNA testing and treated with NA therapy only upon confirmation of HBV reactivation before ALT elevation (level of evidence C1) (6). The use of lamivudine as a universal prophylactic therapy in this subset of patients has to be considered with caution. Benefits have to be pondered with care due to the risk of emergence of lamivudine-resistant mutants (19).

The present study supports the thesis that treatment with anti-TNFα agents is relatively safe regarding the risk of HBV reactivation in anti-HBc positive/HBsAg negative patients. Nonetheless screening for HBV serologic markers prior to initiation of anti-TNFα therapy is of major importance since it may dictate which/ if any actions should be taken to minimize the risks related to hepatitis B infection (prophylactic treatment, vaccination or monitoring).

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PARTE 3: *INFECTION AND MALIGNANCY RISK IN PATIENTS TREATED WITH TNF INHIBITORS FOR IMMUNE-MEDIATED INFLAMMATORY DISEASES*

Infection and malignancy risk in patients treated with TNF inhibitors for immune-mediated inflammatory diseases

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Abstract

Background: Infectious and malignant events are responsible for significant morbidity and mortality in patients with Immune-Mediated Inflammatory Diseases (IMIDs). Anti-tumor necrosis factor (Anti-TNF) agents appear to have an impact, however the individual effect of these agents in the different conditions is still unclear. **Objectives:** To estimate the Incidence Rates (IR) of infections and malignancies in patients treated with anti-TNFs across different IMIDs, as well as potential risk factors, in a Tertiary/University Hospital. **Materials and Methods:** IR/100 patient-years were evaluated in adult patients treated for any IMID with an anti-TNF between January 2000 and December 2014. Data was stratified according to agent, condition and site of infection. Predictor of infections/ malignancy were tested with bivariate and multivariate analysis. **Results:** Three hundred and forty-eight infections [277 (79.6%) non-serious, 71 (20.4%) serious] were reported, during the observational period in 171/387 (44.2%) patients. Thirty-one malignancies were diagnosed in 30/387 (7.8%) patients. Infections and malignancies were responsible for 8.3% and 13.1% of the cases of discontinuation of therapy/anti-TNF switch, respectively. The IR/100 patient-years of serious infections was 4.02 (95% CI 3.20-5.04) ranging from 1.34 (95% CI 0.65-2.74) with etanercept to 6.82 (95% CI 5.12-9.03) with infliximab and from 1.09 (95% CI 0.47-2.52) with psoriatic diseases to 6.63 (95% CI 5.06-8.63) with inflammatory bowel diseases. The most frequent site of serious infection was the gastrointestinal system. Five cases [IR of 0.28 (95% CI 0.12-0.66) per 100 patient-years] of Tuberculosis were diagnosed, all in patients treated with monoclonal antibodies (infliximab and adalimumab). Three (60%) of those cases were extrapulmonary. The IR/100 patient-years of malignancy was 1.75 (95% CI 1.24-2-47) going from 1.17 (95% CI 0.57-2.50) with adalimumab to 2.17 (95% CI 1.30-3.61) with infliximab and from 0.91 (95% CI 0.39-2.11) with inflammatory arthropathies to 2.39 (95% CI 1.34-4.23) with psoriatic diseases. Methotrexate was significantly associated with a decrease in malignant risk in bi- and multivariate analysis. **Conclusion:** There is significant variability in the IR of infections and malignancies across indications and agents. Physicians should be thoughtful when generalizing data from literature regarding the use of an agent in a different indication. Further studies are necessary to clear aspects regarding the safety of individual anti-TNF biologics and to clarify their impact in the different IMIDs.

Introduction

Immune-mediated inflammatory diseases (IMIDs) are a group of highly incapacitating, chronic conditions that share an immune dysregulation caused or accompanied by acute or chronic inflammation, albeit not being clinically related [Kuek et al. 2007; Williams and Meyers 2002]. It is estimated that collectively IMIDs affect 5% to 7% of the population in Western countries [Beyaert et al. 2013]. The treatment of this conditions focuses on the rapid control of inflammation, prevention of tissue damage, with the goal of long-term remission, thus improving quality of life.

Anti-tumor necrosis factor (anti-TNF) therapies were first introduced into clinical practice in 1998 for the treatment of inflammatory bowel diseases (IBDs) and rheumatoid arthritis (RA). Since then anti-TNF biologics were approved for the treatment of several other IMIDs including psoriasis (Ps) and psoriatic arthritis (PsA), ankylosing spondylitis (AS) and juvenile idiopathic arthritis (JIA) changing the treatment and outcome of several of these conditions [Geiler et al. 2011].

Patients with chronic inflammatory diseases have, despite their treatment, an inherently higher risk of infection and malignancy for several disease-related reasons [Beyaert et al. 2013; Doran et al. 2002; Johnston et al. 2013]. There are, nonetheless concerns about the safety of anti-TNF agents which have been present since the introduction of these agents into clinical practice. Even though data concerning this subject is getting more robust from over a decade of treatment for diverse diseases there are still inconsistent results concerning the safety profile. In regard to infectious adverse events, for instance, some reports have shown an increase in the overall serious infection rate [Galloway et al. 2013; Komano et al. 2011] while others denied it [Fouque-Aubert et al. 2010; Leombruno and Keystone 2009; Peyrin–Biroulet et al. 2008]. Additionally, the risk of developing tuberculosis (TB) has been of special concern since TNF has an important biological role in the formation of granuloma and containment of the disease [Senaldi et al. 1996]. Regarding malignancy, earlier studies reported increased risk of lymphoma as well as malignancies overall [Bongartz et al. 2006; Wolfe and Michaud 2004]. On the other hand, more recent studies did not link anti-TNF biologics with an increased risk in solid or hematologic malignancies [Askling 2005a; Askling 2005b; Dommasch et al. 2011; Keystone 2003; Leombruno and Keystone 2009; Moulis et al. 2012; Peyrin–Biroulet et al. 2008; Saad et al. 2010; Wolfe and Michaud 2007b] the exception being melanoma and non-melanoma skin cancer (NMSC) [Askling et al. 2011; Wolfe and Michaud 2007a]. Even so, to the best of the authors' knowledge, studies comparing the infectious/ malignant risk between different IMIDs are lacking [Pereira et al. 2015].

Adverse events such as infusion and injection-site reactions, autoimmunity, heart failure, neurological symptoms, demyelinating disease have also been reported [Chimenti et al. 2014; McLean and Cross 2014; Murdaca et al. 2012]. Even so, the current retrospective observational study describes the experience of a tertiary/university hospital focusing in the development of infectious and malignant adverse events in association with the use of anti-TNF agents.

Materials and methods

This retrospective observational study was conducted in a Tertiary/University Hospital. Patients were identified through each departments' databases. All patients over 18 years old, who had an IMID diagnosis and received at least one month of anti-TNF treatment between January 2000 and December 2014 were included. Data was collected exclusively from the hospital's medical records.

Collected baseline data included patient demographics (gender and date of birth), underlying disease for which the anti-TNF was prescribed, the duration of the disease (defined as the time between diagnosis and the first anti-TNF treatment), smoking status and the presence of any comorbidity. During the observational period each patient could have been treated with one or more anti-TNF agent. Thus, information was gathered regarding every anti-TNF treatment (agent used, starting date, dosage, discontinuation date and along with the reason for cessation), whether switching occurred, the use of concomitant immunosuppressant treatments (corticosteroids, methotrexate, azathioprine et cetera). The anti-TNFs available for treatment during the observational period were Infliximab, Adalimumab, Etanercept and Golimumab. Discontinuation date was defined as the date of the first missed scheduled dose and duration of treatment as the time from initiation of anti-TNF therapy until discontinuation/switch or end of data collection [Dixon et al. 2007]. Furthermore, information from latent tuberculosis (LTB) screening [tuberculin skin test (TST), chest radiography, Interferon-Gamma Release Assays (IGRA)], tuberculosis prophylactic therapy, hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV) viral markers and vaccination (anti-influenza, anti-pneumococcal and others) was acquired.

Adverse events (malignant and infectious) that occurred while the patients were treated with anti-TNF biologics were recorded together with their dates. Data regarding the adverse effects was considered not only when reported in medical records from outpatient visits but also from hospitalizations and emergency department visits. A "serious" infection was defined as any bacterial, viral, or fungal infection that required hospitalization, administration of appropriate intravenous antimicrobial therapy, temporary/ definitive withholding of anti-TNF treatment and/or led to death. Any other infectious event was classified as "non-serious". Infectious events were divided into 5 patterns regarding the site of infection: respiratory tract infections, including upper (nasopharyngitis, sinusitis, pharyngitis, tonsillitis and laryngitis) and lower (pneumonia and bronchitis) tract infections; urogenital infections, including cystitis, urethritis, pyelonephritis, prostatitis, salpingitis and oophoritis, pelvic inflammatory disease and sexually transmitted diseases; skin and soft tissue infections, including cellulitis, abscesses, wound infection, zoster, varicella, pyodermatitis and mycosis; digestive system infections including periapical abscess, oral and esophageal candidiasis, hepatic, intra-abdominal and rectal abscesses. The 5th pattern includes other, less frequently registered, infections such as eye and ear infections, joint and bone infections, neurological infections and septicemia of unknown origin.

Data collection was censored for each patient either at the time of anti-TNF discontinuation, disenrollment from the hospital or at the end of the observation period. This study was approved by the hospital's Institutional Review Board.

Statistical analysis

Regarding descriptive statistics, continuous variables (age, duration of the disease at initiation of anti-TNF and anti-TNF treatment duration) are presented with mean and standard deviation. Frequencies and percentages were used to describe categorical patient characteristics. Incidence rates (IR) of infections, serious infections and malignancy are presented as event/100 patient-years with 95% confidence intervals (95% CI) and were calculated with VassarStats. The distribution of continuous variables were analyzed with the Kolmogorov-Smirnov and Shapiro-Wilk tests to evaluate their deviation from the normal distribution. Continuous were compared using student's t-test or Mann-Whitney U test according to their distribution. Categorical variables were evaluated using Pearson's chi-squared test. A multivariable logistic regression analysis was undertaken to identify independent predictors of infectious and malignant events using the Enter method.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software, version 22.0 and the significance level of 0.05 was considered.

Results

Study population

Since January 2000, a total of 387 patients received at least 1 month of anti-TNF treatment across the different diseases. Three-hundred and twenty-eight patients (84.8%) received only one agent (28.4% etanercept, 30.8% adalimumab and 40.9% infliximab), 59 (15.2%) were treated with a second-line agent (23.7% etanercept, 67.8% adalimumab and 8.5% infliximab). Four (1.0%) patients received adalimumab as a third-line therapy, summing up to 450 treatment courses. Data regarding golimumab was excluded since only 5 patients were treated with that agent.

Table 1 summarizes the baseline characteristics of the study population as a whole and according to the agent used.

Total treatment time was 1777 patient-years with a mean duration of 4.1 years per patient. Almost half of the patients treated had at least one comorbidity, the most common was hypertension (20.9%), dyslipidemia (14.2%) and diabetes (9.3%). Furthermore, 15 patients had a secondary IMID (other than the one for which anti-TNF was indicated). Eight of those cases were psoriasis, 5 ankylosing spondylitis, one Chron's disease and the other ulcerative colitis.

Over half of the patients treated with an anti-TNF for any given IMID underwent, at some point, a combined therapy either with corticosteroids (22.5%) or immunomodulators (59.7%). Triple therapy (anti-TNF + CS + immunomodulator) was administered in 17.3% of the patients. Complemental information is provided in table 2.

Regarding the diseases treated with anti-TNFs, most patients (183) were treated for Inflammatory bowel disease (IBD) followed by patients with Inflammatory arthropathies (excluding psoriatic arthritis) and Psoriatic diseases each with 102 patients. The anti-

Table 1 - Patient baseline characteristics and treatment duration

	Anti-TNF	Etanercept	Adalimumab	Infliximab	p value
Patients	387	120 (26.7%)	156 (34.7%)	174 (38.7%)	
Age in years, mean ± SD	43.2±13.6	46.7±11.7	45.1±12.7	39.2±14.3	ns
Female gender N (%)	221 (57.1)	71 (59.2)	87 (55.8)	105 (60.3)	ns
Disease duration in years, mean ± SD	10.2±10.0	12.9±12.1	11.4±9.9	7.7±7.43	ns
CD N (%)	162 (41.9)	0 (0)	59 (37.8)	123 (70.7)	<0.001
UC N (%)	15 (3.9)	0 (0)	7 (4.5)	12 (6.9)	0.015
IC N (%)	6 (1.6)	0 (0)	1 (0.6)	6 (2.9)	0.033
RA N (%)	57 (14.7)	29 (24.2)	26 (16.7)	10 (5.7)	<0.001
AS N (%)	33 (8.5)	18 (15.0)	16 (10.3)	7 (4.0)	0.005
JIA N (%)	1 (0.3)	1 (0.8)	0 (0)	0 (0)	ns
USpA N (%)	11 (2.8)	7 (5.8)	4 (2.6)	3 (1.7)	ns
Ps+PsA N (%)	48 (12.4)	34 (28.3)	19 (12.2)	3 (1.7)	<0.001
PsA N (%)	18 (4.7)	12 (10.0)	8 (5.1)	2 (1.1)	0.002
Ps N (%)	36 (9.3)	19 (15.8)	16 (10.3)	8 (4.6)	<0.001
Smoking N (%)	92 (23.8)	17 (14.2)	31 (19.9)	48 (27.6)	0.019
Comorbidity N (%)	189 (48.8)	78 (65.0)	77 (49.4)	65 (37.4)	<0.001
Other IMID N (%)	15 (3.9)	2 (1.7)	2 (1.3)	11 (6.3)	0.026
Chronic Pulmonary Disease N (%)	18 (4.6)	8 (6.7)	5 (3.2)	7 (4.0)	ns
Chronic Liver Disease N (%)	4 (1.0)	0 (0)	2 (1.3)	2 (1.1)	ns
Heart Disease N (%)	19 (4.9)	8 (6.7)	5 (3.2)	6 (3.4)	ns
Chronic Kidney Disease N (%)	11 (2.8)	7 (5.8)	4 (2.6)	1 (0.6)	0.023
Osteoporosis Osteopenia N (%)	29 (7.5)	11 (9.2)	14 (9.0)	9 (5.2)	ns
Obesity N (%)	27 (7.0)	8 (6.7)	15 (9.6)	10 (5.7)	ns
Hypertension N (%)	81 (20.9)	38 (31.7)	34 (21.8)	26 (14.9)	0.003
Dyslipidemia N (%)	55 (14.2)	25 (20.8)	26 (16.7)	13 (7.5)	0.003
Diabetes N (%)	36 (9.3)	11 (9.2)	17 (10.9)	13 (7.5)	ns
Treatment duration in years, mean ± SD	4.1±2.7	4.4±2.9	3.9±2.4	3.7±2.8	ns
Total treatment duration in patients-years	1776.7	522.1	599.4	645.3	-

CD **Chron's disease;** UC **ulcerative colitis;** IC **indeterminate colitis;** RA **rheumatoid arthritis;** AS **ankylosing spondylitis;** JIA **juvenile idiopathic arthritis;** USpA **undifferentiated spondyloarthropathy;** Ps **psoriasis;** PsA **psoriatic arthritis**

TNF used was significantly different concerning the disease for which they were prescribed (p<0.001). Over half of IBD patients were treated with Infliximab and none was treated with Etanercept. Regarding psoriatic diseases, on the other hand, 53.7% of patients were treated with Etanecept and Infliximab accounted only for 10.7% of treatments. Patients with inflammatory arthropathies also underwent more treatments with Etanercept (45.5%) followed by Adalimumab (38%) and Infliximab (16.5%)

During the observational period, the reason for suspension/ switch of an anti-TNF treatment, in most patients, was secondary failure of treatment [57/168 (33.9%)]. Furthermore, adverse events accounted for 39.3% of suspension/switch with infectious events and malignancy accounting, respectively, for 21.2%

Table 2 – Adjunctive therapy and vaccinations

	Anti-TNF	Etanercept	Adalimumab	Infliximab
Patients	387	120 (26.7%)	156 (34.7%)	174 (38.7%)
Switch N (%)	60 (15.5)	15 (12.5)	13 (8.3)	37 (21.3)
Combined Therapy N (%)	249 (64.3)	59 (49.2)	89 (57.1)	144 (82.8)
MTX N (%)	121 (31.3)	41 (34.1)	58 (37.2)	47 (27.0)
AZA N (%)	116 (30.0)	0 (0)	26 (16.7)	96 (55.2)
6MP N (%)	1 (0.3)	0 (0)	0 (0)	1 (0.6)
Cy N (%)	5 (1.3)	4 (3.3)	0 (0)	1 (0.6)
MMF N (%)	1 (0.3)	1 (0.8)	0 (0)	0 (0)
CS N (%)	87 (22.5)	26 (21.7)	40 (25.6)	43 (24.7)
CS + Immunomodulator N (%)	67 (17.3)	17 (14.2)	30 (19.2)	37 (21.3)
Influenza vaccine N (%)	188 (48.6)	36 (30)	53 (34.0)	99 (56.9)
Pneumococcal vaccine N (%)	140 (36.2)	21 (17.5)	46 (29.5)	73 (42.0)

MTX **methotrexate**; AZA **azathioprine**; 6MP **6-mercaptopurine**; Cy **cyclosporine**; MMF **mycophenolate mofetil**; CS **corticosteroids**

and 33.3% of the reported adverse events. The appearance of psoriatic skin lesions were the adverse event responsible for suspension/switch in 8 patients (12.1%). On the other hand 13/168 (7.7%) treatments were stopped due to an improvement/ remission of the disease. Information regarding the reason for suspension/switch for each anti-TNF is reported in table 3.

Infections

Vaccination against Influenza and Pneumococcus was administered, at least once, during the treatment period in 188 and 140 patients respectively. However, we did not find a significant reduction in infection rates, even when considering only respiratory tract infections.

No HIV infection was detected in the group of patients treated with anti-TNFs. On the other hand, one patient with chronic HBV and another with HCV infection were treated with biologics. No reactivation occurred with any anti-TNF treatment.

At least one infectious event was reported in 171/387 (44.2%) of the patients and multiple infectious events in 89/387 (23.0 %). A total of 348 infectious events (79.6% non-serious) were described during the observational period resulting in a 19.70 (95% CI 17.91-21.62) per 100 patient-years incidence rate. Most of the infections involved the respiratory tract (36.8%), followed by urogenital (21.0%), skin and soft tissue (20.7%) and digestive system (12.1%) infections. Tables 4 and 5 show the overall rates and infectious patterns.

A total of 71 serious infectious events were diagnosed in 55/387 (14.2%) of the patients during the observational period accounting for a 4.02 (95% CI 3.20-5.04) per 100 patient-years incidence rate. As a group, digestive system infections accounted for the biggest number (22) of serious infections. However, the most commonly reported infection was septicemia of unknown origin (9) followed by pneumonia (8).

When considering individual treatments, the IR of infectious events in patients treated with etanercept was considerably lower, when compared with monoclonal antibodies (p= 0.002), more so when only considering serious infectious events (p

Table 3 - Reason for anti-TNF suspension / switch

	Total	Etanercept	Adalimumab	Infliximab
Patients	168	43 (25.6%)	43 (25.6%)	82 (48.8%)
No data N (%)	19 (11.3%)	6 (14.0%)	6 (14.0%)	7 (8.5%)
Secondary failure N (%)	57 (33.9%)	23 (53.5%)	19 (44.2%)	15 (18.3%)
Disenrollment N (%)	13 (7.7%)	4 (9.3%)	3 (7.0%)	6 (7.3%)
Infection N (%)	14 (8.3%)	1 (2.3%)	2 (4.7%)	11 (13.4%)
Malignancy N (%)	22 (13.1%)	8 (18.6%)	6 (14.0%)	8 (9.8%)
Other adverse effect N (%)	30 (17.9%)	1 (2.3%)	3 (7.0%)	26 (31.8%)
Remission N (%)	13 (7.7%)	0 (0%)	4 (9.3%)	9 (11.0%)

Table 4 - Global infectious events' incidence rates and according to indication

	Anti-TNF		IBD		Psoriatic Disease		Inflammatory arthropathies	
	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)
All infections	348	19.70 (17.91-21.62)	166	22.01 (19.20-25.10)	69	14.98 (12.01-18.53)	113	20.47 (17.31-24.03)
Serious infections	71	4.02 (3.20-5.04)	50	6.63 (5.06-8.63)	5	1.09 (0.47-2.52)	16	2.90 (1.79-4.66)
Site of infection								
Respiratory	128	7.24 (6.12-8.54)	39	5.17 (3.80-6.99)	35	7.60 (5.52-10.39)	53	9.6 (7.41-12.34)
Urogenital	73	4.13 (3.30-5.16)	37	4.91 (3.58-6.69)	11	2.39 (1.34-4.23)	23	4.17 (2.79-6.18)
Skin and soft tissue	72	4.08 (3.25-5.11)	43	5.70 (4.26-7.59)	12	2.61 (1.50-4.50)	16	2.90 (1.79-4.66)
Gastrointestinal	42	2.38 (1.77-3.20)	32	4.23 (3.02-5.92)	5	1.09 (0.47-2.52)	5	0.91 (0.39-2.11)
Others	40	2.26 (1.66-3.06)	20	2.65 (1.72-4.06)	3	0.65 (0.22-1.90)	17	3.08 (1.93-4.88)

<0.002). Furthermore, the infectious patterns vary considerably, with a clear predominance for respiratory infections in patients treated with etanercept and adalimumab whereas patients treated with infliximab have a diversified presentation. Similarly, the IR of infectious events varies with IMIDs. The lowest IR was observed in psoriatic diseases and the highest in IBD.

Bivariate analysis revealed that longer treatment duration [OR 1.153 per each year (95% CI 1.072-1.239), (p<0.001)], female gender [OR 1.503 (95% CI 1.023-2.209), (p=0.038)] and concomitant corticosteroid treatment [OR 1.694 (95% CI 1.097-2.615), (p=0.017)] increased the risk of infection. When considering only serious infectious events, bivariate analysis revealed that none of these factors had an impact on the risk and only IBD (p<0.001) and infliximab (p=0.001) increased the risk, when compared with the other indications and treatments, respectively. However, when the multivariate analysis was performed none remained statistically significant. In fact, when considering the indications separately infliximab only increases the risk of serious infections (p=0.044) in the group of patients treated for inflammatory bowel diseases. Logistic multivariate models confirmed that female gender [OR 1.495 (95% CI 1.005-2.224), (p=0.047)] and treatment duration [OR 1.156 per each year (95% CI 1.074-1.244), (p<0.001)] were independent predictors of infections. The use of corticosteroid treatment almost reached statistical significance [OR 1.532 (95% CI 0.976-2.405), (p=0.064)].

Tuberculosis

A total of 332 (85.8%) patients were screened for latent TB prior to their first anti-TNF. Screening was executed with one or more of the following: TST, chest radiography and/or IGRA which were performed in 278 (71.8%), 275 (71.1%) and 115 (29.7%) patients, respectively. LTB screening was positive in 71/332 (21.4%) patients. Furthermore 86 (22.2%) patients underwent prophylactic TB treatment before the start of the biologic therapy. Prophylactic treatment was

Table 5 - Infectious events' incidence rates according to anti-TNF

	Etanercept		Adalimumab		Infliximab	
	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)
All infections	71	13.6 (10.92-16.81)	140	23.36 (20.15-26.91)	137	21.23 (18.25-24.55)
Serious infections	7	1.34 (0.65-2.74)	20	3.34 (2.17-5.10)	44	6.82 (5.12-9.03)
Site of infection						
Respiratory	36	6.90 (5.03-9.04)	55	9.18 (7.12-11.76)	37	5.73 (4.18-7.80)
Urogenital	12	2.30 (1.32-3.98)	35	5.84 (4.23-8.01)	26	4.03 (2.76-5.84)
Skin and soft tissue	11	2.11 (1.18-3.74)	23	3.84 (2.57-5.07)	38	5.89 (4.32-7.98)
Gastrointestinal	7	1.34 (0.65-2.74)	10	1.67 (0.91-3.05)	25	3.87 (2.63-5.65)
Others	6	1.15 (0.53-2.49)	18	3.00 (1.91-4.69)	16	2.48 (1.53-3.99)

administered in patients when, despite a negative screening, it was deemed clinically appropriate either due to a history of contact or past TB.

During the observational period latent TB was detected in 15 patients, 2 (13.3%) of which had a history of past TB. Regarding pre-treatment screening it was positive in 6/15 (40%) patients that did it. Prophylactic treatment was administered to 7/15 (46.7%) patients. Moreover 5 patients developed active TB, which corresponds to an IR of 0.28 (95% CI 0.12-0.66) per 100 patient-years. Four of the cases developed with infliximab [IR 0.62 (95% CI 0.24-1.58) per 100 patient-years], the other one, with adalimamab [IR 0.17 (95% CI 0.03-0.94) per 100 patient-years]. Three (60%) of the cases were extra pulmonary (miliary TB, tuberculous adenitis and nasal tuberculosis). None of them had a past history of TB and 4 (80%) of them were screened with negative pretreatment screening.

Malignancy

Among the 387 anti-TNF treated patient, 31 malignancies were diagnosed during the observational period, corresponding to an IR of 1.75 (95% CI 1.24-2-47) per 100 patient-years. Both solid (28) and hematologic (3) malignancies occurred. Regarding solid tumors, sites afflicted included oropharyngeal (3), colorectal (5), hepatobiliary (1), lung (1), breast (4), cervix (1), prostate (1), kidney (1), urinary bladder (1), melanoma (1), non-melanoma skin (4), brain (2) and endocrine glands (3). One specific patient was diagnosed with 2 different malignancies during the observational period. Furthermore, 5 patients had a history of malignancy prior to the anti-TNF therapy. None of them was diagnosed with a relapse of their original malignancy / developed a new malignancy.

The IR of malignant events was 1.99 (95% CI 1.21-3.26) per 100 patient-years in patients with IBD and 2.39 (95% CI 1.34-4.23) per 100 patient-years in patients with psoriatic disease, over two-fold higher than in patients with inflammatory arthropathies [0.91 (95% CI 0.39-2.11) per 100 patient-years]. Regarding the anti-TNF agent used during the diagnosis of the malignancy, both etanercept [1.92 (95% CI 1.05-3.50) per 100 patients-years] and infliximab [2.17 (95% CI 1.30-3.61) per 100 patients-years] had higher incidence rates than adalimumab [1.17 (95% CI 0.57-2.50) per 100 patients-years].

Compared with the remaining patients treated with anti-TNFs, the 30 patients that developed a malignant tumor were older (mean age: 50.8 vs 42.6 years) at the time of starting the biologic treatment [OR 1.048 per each year (95% CI 1.018-1.080), (p=0.001)], as expected from the occurrence of malignancies in the general population, and, surprisingly, were characterized by a lower prevalence of combined therapy [OR 0.382 (95% CI 0.181-0.810, (p=0.010)], particularly methotrexate [OR 0.127 (95% CI 0.030-0.541), (p=0.001)]. Logistic multivariate analysis confirmed the increased risk of malignancy with age [OR 1.053 per each year (95% CI 1.021-1.085), (p=0.001)] and that the decreased risk observed with combined therapy was due to methotrexate [OR 0.110 (95% CI 0.024-0.518), (p=0.005)] and not any adjunctive therapy (p=0.833).

Discussion

The aim of this retrospective study was, to evaluate, in a real-world setting, the incidence of infectious and malignant events in patients, with different IMIDs, treated with anti-TNF agents. Information regarding infection and cancer patterns as well as potential risk factors, with particular focus on the role of the different agents and conditions were addressed.

Infections

Infectious events were reported in a significant number of the patients (44.2%). Non-serious infections accounted for 79.6% of total infections even though the real number must be significantly higher due to the underreporting bias inherent to the study design.

Serious infections were experienced by 55 (14.2%) of the patients, exceedingly higher than the one found in a meta-analysis of randomized control trials (0.61%) [Dommasch et al. 2011]. Notwithstanding, similar retrospective studies reported considerably lower rates than this study [Curtis et al. 2007a; Favalli et al. 2009; Komano et al. 2011]. The overall IR of serious infections was 4.02 (95% CI 3.20-5.04) per 100 patient-years incidence rate. An similar retrospective study reported an analogous IR [Favalli et al. 2009]. Nonetheless, several observational studies found, to different degrees, higher rates of serious infections [Dixon et al. 2006; Komano et al. 2011; Kroesen et al. 2003; Lichtenstein et al. 2012; Salliot et al. 2007]. Some variability may be explained by different definitions of serious infections and length of observational periods through different studies in addition to some underreporting bias.

When considering overall infections, the most common sites involved were the respiratory tract followed by urogenital and skin and soft tissue. However, when only considering serious infections, digestive system infections prevail which is at odds with most literature where the patterns are similar to the one found overall [Dixon et al. 2006; Germano et al. 2014; Komano et al. 2011; Listing et al. 2005; Salliot et al. 2007]. Most studies were made in patients with RA and spondyloarthropathies, thus these results could be explained by the inclusion of patients with IBD that may have distinct infectious patterns [Ananthakrishnan and McGinley 2013; Deepak et al. 2013; Nanau et al. 2014]. In this study, like in previously published literature, infliximab and adalimumab have higher incidence rates of serious adverse events, when compared with etanercept [Curtis et al. 2007b; Favalli et al. 2009; Girolomoni et al. 2012]. Even though others found similar rates across the different agents [Dixon et al. 2006; Listing et al. 2005]. Previous studies hinted that patients with psoriasis have lower rates of serious infectious events than those with RA [Moreland et al. 2001; Tyring et al. 2007]. In fact, in this study it was observed a higher IR in patients with IBD and inflammatory arthropathies than in those with psoriatic diseases although it cannot be said that it is due to disease since there are some prescription bias with a preponderance of infliximab in patients with IBD and etanercept in psoriatic diseases in addition to dissimilar use of other immunosupressants.

Regarding the risk factors for serious infection, the only factors that were statistically increased the risk, in the bivariate analysis, were treatment with

infliximab and inflammatory bowel disease yet multivariate analysis tear down that hypothesis, reinforcing the need for clarification of individual risk of the different diseases and agents.

Tuberculosis

The IR of active tuberculosis, in the Portuguese general population, was 25 (22-28) per 100.000 population in 2015 [2015]. Portugal is a country with high TB prevalence, nonetheless, an IR approximately 10-fold higher was found in this group of patients treated with anti-TNFs. These numbers should be assessed taking into consideration the fact that pretreatment screening is largely engaged. In fact 80% of the patients that had active TB while being treated, had a negative pretreatment screening. A previous study in Spain reported similar findings and hypothesized that the use of other immunosuppressants at time of the screening tests lead to false negatives results [Jauregui-Amezaga et al. 2013]. Moreover, studies in areas with a much lower TB incidence also report disproportionate TB rates in patients under anti-TNF [Favalli et al. 2009]. All cases of active TB were diagnosis in patients treated with infliximab and adalimumab, hence no case of active TB was diagnosed in patients treated with etanercept. These findings are in line with larger studies that show a significantly higher risk of TB in patients treated with monoclonal antibodies [Dixon et al. 2010a; Tubach et al. 2009; Wallis et al. 2004]. Sixty percent of the tuberculosis diagnosis were extrapulmonary which is in accordance with previous studies that consistently report extrapulmonary TB in over 50% of active TB cases [Alawneh et al. 2014; Dixon et al. 2010a; Jauregui-Amezaga et al. 2013].

Malignancy

Overall, the IR of malignancy [1.75 (95% CI 1.24-2-47) per 100 patient-years] was substantially higher than the general Portuguese population [0.4419 per 100 population in 2010] [RORENO 2016]. Previous studies have demonstrated similar findings, in different populations [Berghen et al. 2015; Chiesa Fuxench et al. 2016; Raaschou et al. 2016]. Although there is some concern, particularly with lymphomas and NMSC, recent data from meta-analyses and registers, seem to indicate that treatment with anti-TNF biologics does not increase the risk of malignancy whether in IBD, psoriatic disease or inflammatory arthropathies [Askling et al. 2009a; Askling et al. 2011; Buchbinder et al. 2015; Dommasch et al. 2011; Huang et al. 2011; Kimball et al. 2014; Moulis et al. 2012; Pedersen et al. 2010; Peyrin–Biroulet et al. 2008; Williams et al. 2014; Zhang et al. 2013]. The reported incidence rates, over two-fold higher in patients with IBD and psoriatic disease when compared with inflammatory arthropaties, are reasonable since previous studies implicate that disease-related factors, and not the treatment, may impact the risk of malignancy [Baecklund et al. 2006; Kimball et al. 2014; van Lumig et al. 2015]. A meta-analysis of randomized control trials described an IR of 1.273 malignancies per 100 PA in different conditions [Askling et al. 2011]. This study results are higher than those of RCTs most likely due to the longer observation period. When considering the anti-TNFs individually, the same meta-analysis reported the opposite finding: the IR of

patients treated with adalimumab was higher than those treated with etanercept and infliximab (1.423 vs 1.160 and 1.228 per 100 PA). On the other hand, data from clinical trials with adalimumab revealed an IR very similar to this study [Burmester et al. 2013]. Data regarding malignancy rates is still scant and population related factors may have a strong impact, especially when considering individual agents with different studies reporting discordant results [Askling et al. 2009b; Bongartz et al. 2009; Kievit et al. 2011; Kimball et al. 2014; Okada and Siegel 2006].

Regarding the treatment of patients with a history of cancer, no malignancy was reported in the 5 cases present. Studies in patients with IBD admit that such patients are at increased risk of new or recurrent cancers even though anti-TNFs have a minor/ no contribution to the increased risk [Axelrad et al. 2016; Beaugerie 2013; Dixon et al. 2010b; Poullenot et al. 2016].

Concerning risk factors for malignancy, the present study found that age, but not disease duration, increased the risk of a malignant event. These results suggest a malignancy-protective effect of methotrexate. Albeit not being reported previously [Krathen et al. 2010; Salliot and van der Heijde 2009], theoretically such an effect is possible since, in addition to the immunosuppressant effect for which it is used in IMIDs, methotrexate is used in the treatment of several cancers due to its antineoplastic effect.

The results of this study should take in considerations the limitations inherent to the study design. The data collected was based on hospital records so ascertainment bias, lack of relevant information, misclassification, and channeling are probable limitations of the study. The sample size and observation period must be taken in consideration when considering the incidence of rare adverse events such as cancer or serious infections, more so when breaking down into disease or treatment. Furthermore, preceding treatments (other than anti-TNF) were disregarded although they may have some implications. Further limitations specific to the study stemmed from the inclusion of different IMIDs. Data was collected from patients across 9 different anti-TNF indications that more than accounting for some heterogeneity, prevented us from using classifications of disease severity that would be unapproachable. Moreover, another simplification was employed by encompassing the diseases in 3 groups (IBD, Inflammatory arthropathies and Psoriatic diseases). Additionally, guidelines regarding anti-TNF treatment varied between departments and through the 10 years of anti-TNF treatment in the authors' hospital which may account for some variability regarding pretreatment screening/ prophylaxis.

Summing up, anti-TNF biologics are widely used in the treatment of IMIDs, particularly in RA, IBD and psoriatic diseases. Albeit some safety concerns, they are a powerful therapeutic weapon that allow the control of, above all, severe presentations of this conditions.

Physicians, never the less, should be aware that anti-TNFs may increase the risk of infections that could have severe consequences. On the subject of TB, despite active screening, it continues to be an important problem in patients treated with anti-TNF biologics, especially in parts of the world with a high

background TB prevalence. Current evidence is not robust enough to exclude anti-TNFs from having an impact in the overall risk of malignancy thus tight surveillance should be employed in everyday practice. Caution in generalizing data from the literature should be employed, since the safety profile of these agents may be substantially altered depending on the disease for which they are used. Hence, future studies/ registries should be developed, evaluating longer follow-up durations, ideally matching anti-TNF naïve populations, in order to further elucidate the risk of individual anti-TNF treatments in the different IMIDs.

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PARTE 4: *POSTER* APRESENTADO NAS XXVIII JORNADAS DE TERAPÊUTICA

Segurança de terapêuticas anti-TNF em doenças inflamatórias imunomediadas foco nas infeções e neoplasias

Rui Pereira[1] orientado por Tiago Torres[1,2]

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INTRODUÇÃO

As doenças inflamatórias imunomediadas englobam um vasto grupo de doenças crónicas que partilham alterações do sistema imunológico causadas por ou acompanhadas de inflamação aguda ou crónica. Os inibidores do fator de necrose tumoral (anti-TNF) são um grupo de agentes biológicos que revolucionaram o tratamento de muitas destas doenças ainda que não sejam livres de efeitos adversos.

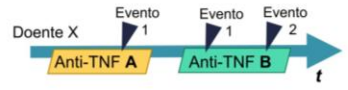
As infeções e neoplasias são responsáveis por morbimortalidade significativa em indivíduos com doenças inflamatórias imunomediadas. Os agentes anti-TNF parecem, ter influência nestes eventos, particularmente na tuberculose. No entanto, o efeito individual de cada agente nas diferentes doenças é pouco claro [1].

OBJETIVOS

- Descrever a incidência de eventos infeciosos e malignos em doentes tratados com anti-TNF na prática diária de um hospital terciário;
- Testar potenciais preditores de infeções/neoplasias;
- Comparar diferentes agentes e patologias.

MATERIAIS E MÉTODOS

Análise retrospetiva de processos clínicos de adultos tratados com anti-TNF em dermatologia, gastrenterologia e/ou imunologia clínica no CHP desde janeiro 2000 até dezembro 2014 (mínimo 1 mês de tratamento).



Esquema 1 - Recolha de dados num determinado doente

DADOS RECOLHIDOS

- Dados demográficos, doença para a qual o anti-TNF foi prescrito, anti-TNF prescrito (infliximab, adalimumab, etanercept), duração da doença, tabagismo, comorbilidades e antecedentes de relevo. Tratamentos imunossupressores concomitantes, rastreios pré-tratamento e vacinas.

Esquema 2 - Eventos registados ao longo do período de observação

A análise estatística foi realizada no SPSS 22.0 considerando uma significância de 0,05. A distribuição das variáveis contínuas foi analisada com os testes de *Kolmogorov-Smirnov* e *Shapiro-Wilk*. Variáveis com distribuição normal foram avaliadas com o *t-test* e as restantes com o teste de *Mann-Whitney*. As variáveis categóricas foram avaliadas por meio do teste do qui-quadrado de *Pearson*. A regressão logística multivariada foi realizada para identificar os preditores independentes de eventos adversos usando o método *Enter*. As taxas de incidência são apresentadas na forma de eventos/100 doentes-ano com intervalo de confiança de 95% (IC 95%) e foram calculadas com o software VassarStats.

RESULTADOS

Ao longo do período observacional **387** doentes preencheram os critérios de inclusão e **450** tratamentos anti-TNF foram administrados. O tempo total de tratamento foi 1777 doentes-ano e o tempo médio de tratamento foi **4,1 anos** por doente.

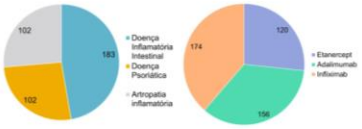


Gráfico 1 - Número de doentes e tratamentos durante o período observacional

Mais de metade (**64.3%**) dos doentes receberam tratamento combinado. Imunomoduladores foram administrados em 59.7% dos doentes, corticosteroides em 22.5% e terapia tripla em 17.3%.

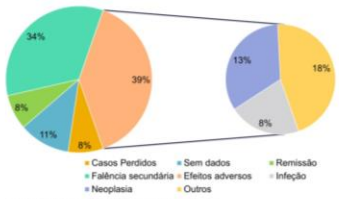


Gráfico 2 - Razão para a suspensão ou *switch* de anti-TNF

INFEÇÕES

Um total de **348** infeções, **14.2%** das quais graves, foram reportadas em 171 doentes (44.2%). Estes valores correspondem a uma taxa de incidência de **19.70** (17.91-21.62) para infeções e **4.02** (3.20-5.04) para infeções graves.

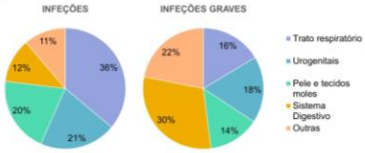


Gráfico 3 - Frequência dos diferentes tipos de infeções

Na análise multivariada o género feminino [OR 1.495 (IC 95% 1.005-2.224) (p=0.047)], e a duração do tratamento [OR 1.156 por cada ano (IC 95% 1.074-1.244) (p<0.001)] mostraram-se preditores independentes de infeção. Não foram detetados preditores independentes de infeção grave.

Tuberculose

Antes da primeira administração de um anti-TNF 332 doentes (**85.8%**) foram rastreados para tuberculose latente e 86 (**22.2%**) receberam tratamento profilático.

Contudo tuberculose ativa foi diagnosticada em 5 doentes correspondendo a uma taxa de incidência de **0.28** (0.12-0.66) sendo que **4** destes casos tinham rastreio pré-tratamento negativo.

Todos os casos registados ocorreram em doentes tratados com anticorpos monoclonais (4 com infliximab e 1 com adalimumab).

Três dos casos (60%) foram doença extrapulmonar.

NEOPLASIAS

No período observacional foram diagnosticadas **31** neoplasias malignas traduzindo-se numa taxa de incidência de **1.75** (1.24-2.47). A análise multivariada mostrou que a idade [OR 1.053 por cada ano (IC 95% 1.021-1.085) (p=0.001)] aumenta o risco de neoplasia ao contrário do tratamento com metrotexato que parece reduzi-lo OR 0.110 (IC 95% 0.024-0.518) (p=0.005)].

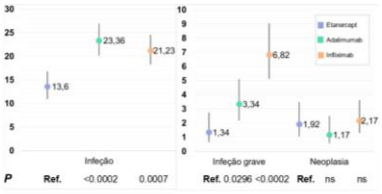


Gráfico 5 - Taxas de incidência por agente (Ref.) categoria de referência (ns) não significativo

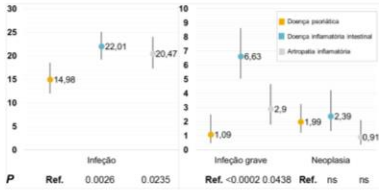


Gráfico 6 - Taxas de incidência por patologia (Ref.) categoria de referência (ns) não significativo

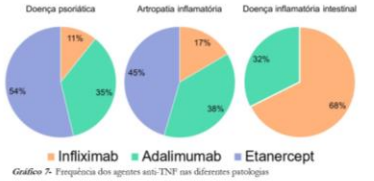


Gráfico 7 - Frequência dos agentes anti-TNF nas diferentes patologias

CONCLUSÕES

- As infeções e neoplasias têm um impacto importante nos doentes tratados com agentes anti-TNF;
- As infeções graves e neoplasias malignas são eventos raros. Como o período observacional foi alargado, registamos taxas de incidência superiores às observadas em ensaios clínicos randomizados [5];
- A taxa de incidência de tuberculose no nosso estudo é cerca de 10 vezes superior à taxa de incidência da população geral portuguesa com a agravante que a maioria dos doentes realizou rastreio de tuberculose latente [3]. As formas de tuberculose extrapulmonar são as mais frequentes [4];
- O tratamento com metotrexato, ao contrário do que estava descrito anteriormente na literatura, teve um efeito protetor quanto ao risco de neoplasia [5];
- Existem diferenças significativas nas taxas de infeção tendo em conta os agentes e as patologias, como já publicado anteriormente [6,7].
- Apesar de existirem preocupações de segurança, os agentes anti-TNF são uma poderosa arma terapêutica que permitem o controlo das apresentações mais graves destas patologias. São, no entanto necessários mais estudos para clarificar qual o impacto atribuível aos agentes e à patologia de base;

Agradecimentos

Prof. Dr. Tiago Torres, Prof. Dra. Margarida Lima,

Dra. Isabel Fonseca, Mafalda Laranjo e Joana Moreno

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[1]Pereira et al. Drug Dev Res. 2015;76(8):419-27.
[2]Dommasch et al. J Am Acad Dermatol. 2011;64(6):1035-50.
[3]Global tuberculosis report 2015. WHO.
[4]Dixon et al. Ann Rheum Dis. 2010;69(3):522-8.
[5]Salliot et al. Ann Rheum Dis. 2009;68(7):1100-4.
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CONCLUSÃO

O objetivo deste projeto foi avaliar a incidência de infeções e neoplasias em doentes com diferentes doenças inflamatórias imunomediadas tratados com agentes anti-TNF, em condições de prática clínica. Foram ainda abordados os tipos de infeções e neoplasias, potenciais fatores de risco, com particular destaque para o papel dos diferentes agentes e patologias.

Neste estudo foi avaliada uma amostra de tamanho significativo: 387 doentes (450 tratamentos anti-TNF diferentes) com um tempo total de tratamento de 1777 doentes-ano. Ao longo deste período observacional foram registadas infeções em 44.2% e infeções graves em 14.2% dos doentes correspondendo a taxas de incidência de 19.70 (IC 95% 17.91-21.62) e 4.02 (IC 95% 3.20-5.04) por 100 doentes-ano, respetivamente. Estas taxas estão muito provavelmente subvalorizadas.

Está preconizada a realização de um rastreio pré-tratamento da tuberculose latente, VIH, hepatite B e C, entre outros, de modo a que as medidas necessárias possam ser tomadas.

Relativamente à infeção da hepatite B, é aceite que as terapêuticas anti-TNF têm risco de reativação da doença crónica. Contudo, no que toca aos doentes com serologias compatíveis com infeção passada, o risco conferido pelas terapêuticas anti-TNF não é claro. Nesta série de doentes, observaram-se 26 casos compatíveis com infeção passada sendo que nenhuma reativação foi registada. Outras séries admitem que a reativação é possível neste grupo de doentes, apesar de ser muito menos comum do que em doentes com infeção crónica pelo vírus da hepatite B. Por outro lado, apesar de existir um protocolo de rastreio da hepatite B no CHP este, frequentemente, não é cumprido (75% dos doentes rastreados).

A tuberculose é das principais preocupações em doentes expostos a agentes anti-TNF pois estes têm maior risco de reativação da doença latente. Para além disso, a tuberculose é mais frequentemente atípica, extrapulmonar ou disseminada estando presente mesmo em doentes com rastreio da tuberculose latente negativo. Portugal é um país com alta prevalência de TB, no entanto, a taxa de incidência deste estudo [0.28 (IC 95% 0.12-0.66) por 100 doentes-ano] é aproximadamente 10 vezes superior à da população portuguesa. Estes números devem ser avaliados tendo em conta o facto de que na maioria destes doentes (86%) foi realizado um rastreio pré-tratamento. Este estudo mostra resultados concordantes com a literatura: formas extrapulmonares mais frequentes (60%), maior risco com anticorpos monoclonais (100%) e casos em doentes com rastreio pré-tratamento

negativo (80%).

Relativamente às neoplasias, foram registados 31 casos [taxa de incidência de 1.75 (IC 95% 1.24-2.47) por 100 doentes-ano]. Em relação ao tratamento com agentes anti-TNF em doentes com antecedentes de neoplasias, foram detetados 5 casos neste estudo, onde nenhuma recidiva ou neoplasia de novo foi detetada. Vários estudos conjeturam que o risco de recidiva ou aparecimento de neoplasias está mais relacionado com a atividade inflamatória destas patologias e que os anti-TNF tem um contribuição reduzida ou nula para o aumento do risco. Algo que não estava descrito anteriormente na literatura e que foi evidente neste grupo de doentes, foi o facto da terapia combinada com metotrexato parecer reduzir o risco de neoplasia. Tal pode ser explicado pelo seu efeito antineoplásico, motivo pelo qual é utilizado no tratamento de diversas neoplasias.

As taxas de incidência dos eventos infeciosos e neoplásicos são similares às reportadas em estudos com desenho semelhante. A importância destes acontecimentos é evidente quando se verifica que a principal causa para a interrupção das terapêuticas anti-TNF são os efeitos adversos e mais de metade destes são neoplasias ou infeções.

Doenças caracterizadas por inflamação crónica têm um risco inerente de infeção e neoplasias por várias razões relacionadas com a doença e não apenas pelo tratamento. Este estudo mostrou que os doentes tratados com anticorpos monoclonais têm taxas de incidência de infeções graves superiores aos tratados com etanercept, como já publicado anteriormente. Algo semelhante é, contudo, verificado quando as taxas de incidência são comparadas por indicação. Os doentes tratados por doença psoriática têm menor taxa de incidência de infeções graves quando comparados com as restantes indicações.

Existe uma variabilidade significativa na taxa de incidência de infeções e doenças malignas de acordo com as diferentes indicações e agentes. A generalização de dados da literatura sobre o uso de um agente numa determinada patologia pode ser incorreta. Mais estudos são necessários para esclarecer aspetos relacionados com a segurança individual dos agentes anti-TNF e clarificar o seu impacto nas diferentes doenças inflamatórias imunomediadas.

Em suma, os tratamentos anti-TNF são relativamente seguros se as precauções apropriadas forem tomadas. Para evitar os efeitos adversos o médico deve estar ciente das complicações possíveis e das recomendações de rastreio e follow-up dos doentes tratados com estes agentes.

APÊNDICE

Proposta de projeto de investigação

Academic research project

Safety of anti-TNF therapies in immune-mediated inflammatory diseases: focus on infections and malignancy

Student

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Sponsor: Prof. Dr. Margarida Lima, HSA/CHP e ICBAS/UP

Tutor: Tiago Torres, CHP – HSA

Academic years: 2014/2015 and 2015/2016

INDEX

Abstract

Introduction: Immune-mediated inflammatory diseases are estimated to affect 5% to 7% of the population in Western countries. One of the emerging therapies against this diseases are biologics. This biologics are use in a great number of patients and a diverse group of pathologies and there have always been safety concerns regarding these drugs. Anti-tumor necrosis factor has significantly changed the treatment and outcome of several inflammatory diseases as Rheumatoid Arthritis, inflammatory bowel disease and Psoriasis however concerns regarding the safety and efficacy of these agents have been raised.

Objectives: In this study we intend to investigate the incidence, as well as the prevalence of infections and malignancy in patients with IMIDs treated with anti-TNF as currently there is no information regarding anti-TNF therapies and its adverse effects in Portugal.

Materials and Methods: This retrospective observational study will be conducted in CHP. The patients that received anti-TNF agents for the treatment of IMIDs will be included.

Resumo

Introdução: Estima-se que no seu conjunto as doenças inflamatórias imunomediadas afectem 5 a 7% da população dos países ocidentais. Uma das terapêuticas emergentes usadas contra este grupo de doenças são os agentes biológicos. Estes fármacos são usados num grande número de doentes bem como num diverso grupo de patologias e sempre existiram preocupações com a segurança destes agentes. Os biológicos anti-TNF alteraram de um modo significativo o tratamento e prognóstico de doenças como a Artrite Reumatoide, doença inflamatória intestinal e psoríase contudo continuam a existir preocupações com a segurança e eficácia destes agentes.

Objetivos: Neste estudo pretende-se investigar a incidência, bem como a prevalência de infeções e neoplasias em pacientes com doenças inflamatórias imunomediadas tratados com biológicos anti-TNF visto que atualmente não há qualquer informação relativamente a terapêuticas anti-TNF e os seus efeitos adversos em Portugal.

Materiais e Métodos: Este estudo observacional retrospetivo irá ser conduzido no CHP. Serão incluídos os adultos que receberam biológicos anti-TNF para o tratamento de uma doença inflamatória imunomediada.

RESEARCH PROJECT PROPOSAL

Introduction

Immune-mediated inflammatory diseases (IMIDs) are defined as a group of chronic and highly incapacitating conditions that are not clinically related but share an immune dysregulation caused or accompanied by acute or chronic inflammation [1,2]. They are estimated to affect 5% to 7% of the population in Western countries [3] and their treatment focuses on the rapid control of inflammation, prevention of tissue damage, with the goal of long-term remission of the disease, thus improving quality of life. The primary therapeutic assets available are corticosteroids, immunosuppressants, and biologic agents, especially those targeting tumor necrosis factor (TNF) [3].

Anti-tumor necrosis factor (anti-TNF) therapies were first introduced into clinical practice in 1998 for the treatment of inflammatory bowel diseases and Rheumatoid Arthritis. Thenceforth they have significantly changed the treatment and outcome of several inflammatory diseases [4]. It is generally known that patients with chronic inflammatory diseases have a higher risk of infection and malignancy for several disease-related reasons [3,5,6]. Presently there are some concerns regarding the safety and efficacy of these agents although the data concerning this subject is getting more robust amongst more than a decade of treatment for diverse diseases. Even so, different studies have had inconsistent results concerning the safety profile. Some reports have revealed an increase in the overall serious infection rate [7,8], while others stated that there is no significant increase in serious infections [9-11]. The increased risk of developing tuberculosis has been of special concern since TNF has an important biological role in the formation of granuloma and containment of the disease [12]. In regard to malignancy, earlier studies reported increased risk of lymphoma and malignancies overall [13,14]. However more recent studies do not associate anti-TNF biologics with an increased risk in solid or hematologic malignancies [9,10,15-21] with the exception of melanoma and non-melanoma skin cancer (NMSC) [22,23].

The aim of this research project is to survey information available in Centro Hospitalar do Porto (CHP) regarding anti-TNF therapies and focusing on infections and malignancy, as concerning and life threatening adverse effects, in CHP's patients treated in the following diseases: Psoriasis (Ps) and Psoriatic Arthritis (PsA), Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Juvenile Idiopathic Arthritis (JIA) and inflammatory bowel diseases (IBD), such as Crohn's Disease (CD) and Ulcerative Colitis (UC).

The investigators are aware that as this study is observational, retrospective as well as lacking a control population and with a limited number of patients no information will be produced regarding the relative risk of intercurrences. Nonetheless our objective is to compare our data with previously published studies thus assessing our reality.

Clinical problems

There is no information regarding patients with IMIDs treated with anti-TNF therapies in Portugal. This biologics are use in a great number of patients and a diverse group of pathologies and there have always been safety concerns regarding these drugs.

Research questions

What is our reality?
What is the incidence of infection and malignancy in our patients treated with anti-TNF?
What is the prevalence of infections and malignancy in this group of patients?

Research goals

In this study we intend to investigate the incidence, as well as the prevalence of infections and malignancy in patients with IMIDs treated with anti-TNF.

Contributors

Institutions, Departments and Services

- Centro Hospitalar do Porto (CHP).
  - Hospital de Santo António (HSA).
    - Departamento de Medicina (DM).
      - Serviço de Dermatologia (SD), Serviço de Gastrenterologia (SG) e Unidade de Imunologia Clínica (UIC).

Research Team

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Student

Rui Pereira: medical student, Disciplina de Iniciação à Investigação Clínica (DIIC), Mestrado Integrado em Medicina (MIM), ICBAS/UP

Other researchers

- Paula Lago, M.D.: Serviço de Gastrentologia, Centro Hospitalar do Porto.
- Raquel Faria, M.D.: Unidade de Imunologia Clínica, Centro Hospitalar do Porto.

Tutor

- Tiago Torres, M.D., Ph.D.: Serviço de Dermatologia, Centro Hospitalar do Porto, Unit for Multidisciplinary Research in Biomedicine – ICBAS/UP, Dermatology Research Unit, Centro Hospitalar do Porto.

DIIC Supervisor

- Margarida Lima: M.D., Ph.D., invited professor, ICBAS/UP;

Roles and responsibilities

- The conception and development of the proposal and the project's execution are the responsibility of the student;
- The Tutor will chaperon the student in the development of the proposal and in the project's execution and the analysis and interpretation of the results.
- The Supervisor will manage all the project's phases from its conception, execution, data analysis to the presentation of the results.

Time allocated to the project

First and last name	Function	% Time allocated to the project	N of months	People * Month
Rui Pereira	Student	10	22	2,20
Tiago Torres	Tutor	2,5	22	0,55
Paula Lago	Researcher	2,5	22	0,55
Raquel Faira	Researcher	2,5	22	0,55
Margarida Lima	Supervisor	2,5	22	0,55
			Total	4,40

Conditions and motivations for the development of the project

Installed capacities and available resources

For the development of this project it will be necessary access to clinical records (material and digital) so a space with capacity for the analysis of this material will be required.

Investigation team merit

Tiago Torres, Paula Lago and Raquel Faria have both clinical and investigational experience in the project's area.

Personal motivations for the development of the project

The personal motivations in integrating a team for the development of a project start from the lack of opportunities in our degree to accomplish and learn the processes of a clinical investigation. As to the area, Dermatology was chosen because in my classes with Dr. Tiago Torres I got to know a little about psoriasis and understood that there was a lot of investigation in that area and that it was a lot more extensive.

Methodology

Literature review criteria

For the literature review B-On was employed as a means to access the articles researched was in Medline via PubMed. English articles were searched with the following keywords: safety, adverse event, immune-mediated inflammatory diseases, anti-TNF, psoriasis, inflammatory bowel disease, rheumatoid arthritis, infection, malignancy, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn's disease and ulcerative colitis. The search results were then supplemented by including documents suggested by authors' experience.

Project design

Project type

Clinical research, institutional, analytical observational and longitudinal (retrospective), cohort study with a clinical scope.

Universe, population and sample

Universe:

Adult patients treated with anti-TNF.

Population:

Adult patients treated with anti-TNF in Dermatology, Gastroenterology or Clinical Immunology in CHP.

Sample:

Size intended for the sample: 400 patients (all the adult patients treated with anti-TNF in the above mentioned medical departments).

Participant selection

Elegebility criteria

Inclusion criteria

Adult patients treated with anti-TNF therapeutics in Dermatology, Gastroenterology or Clinical Immunology in CHP since January 2000 until February 2015.

Exclusion criteria

Patients with missing information will be excluded.

Project plan

Project related tasks

Task list:

During the project's execution the following tasks are foreseen:

Task 1: Participant selection	
Duration:	1 month
Foreseen dates for the beginning and conclusion:	05/01/2015 – 30/01/2015
Institutions, Departments and Services:	CHP – HSA – DM: SD, SG and UIC
Objectives:	Select participants for data recovery.
Description:	Cases will be selected form the different departments with regard to the inclusion/exclusion criteria.
Involved investigators:	Dr. Tiago Torres, Dr. Paula Lago and Dr. Raquel Faria
Investigators functions and responsibilities:	Dr. Tiago Torres is responsible for the selection in Dermatology, Dr. Paula Lago in Gastroenterology and Dr. Raquel Faria in Immunology.

Task 2: Data recovery	
Duration:	4 months
Foreseen dates for the beginning and conclusion:	16/02/2015– 26/06/2015
Institutions, Departments and Services:	CHP – HSA – DM: SD, SG and UIC
Objectives:	Collect the data for the study.
Description:	Fill the data recovery sheet with the available information in the physical and informatics process for every selected case.
Involved investigators:	Dr. Tiago Torres and Rui Pereira
Investigators functions and responsibilities:	Dr. Tiago Torres will overlook Rui Pereira in the data recovery.

Task 3: Database construction	
Duration:	1 month
Foreseen dates for the beginning and conclusion:	29/06/2015– 31/07/2015
Institutions, Departments and Services:	CHP – HSA – DM: SD, SG and UIC
Objectives:	Construction of the database for the data analysis.
Description:	The data collected will be inputted in a spreadsheet in SPSS for posterior data analysis,
Involved investigators:	Rui Pereira
Investigators functions and responsibilities:	Rui Pereira is solely responsible for this task.

Task 4: Data analysis	
Duration:	1 month
Foreseen dates for the beginning and conclusion:	01/09/2015– 30/09/2015
Institutions, Departments and Services:	CHP – HSA – DM: SD, SG and UIC
Objectives:	Analyze the recovered data.
Description:	The data obtained will be analyzed with SPSS and the relevant data will be selected for presentation.
Involved investigators:	Rui Pereira
Investigators functions and responsibilities:	Rui Pereira with the help of Professor Isabel Fonseca will analyze the data.

Task 5: Review article	
Duration:	5 months
Foreseen dates for the beginning and conclusion:	03/11/2014– 27/03/2015
Institutions, Departments and Services:	CHP – HSA – DM: SD, SG and UIC
Objectives:	Publishing of a Review article.
Description:	A bibliographic review will be accomplished and a review article for publishing structured.
Involved investigators:	Dr. Tiago Torres and Rui Pereira
Investigators functions and responsibilities:	Rui Pereira is responsible for the development of the article. Dr. Tiago Torres will oversee and audit the article.

Task 6: Original article	
Duration:	3 months
Foreseen dates for the beginning and conclusion:	05/10/2015– 01/01/2016
Institutions, Departments and Services:	CHP – HSA – DM: SD, SG and UIC
Objectives:	Publishing of an Original article.
Description:	The results will be constructed into an original article for publishing.
Involved investigators:	Dr. Tiago Torres and Rui Pereira
Investigators functions and responsibilities:	Rui Pereira is responsible for the development of the article. Dr. Tiago Torres will oversee and audit the article.

Task 7: Oral presentation of the project	
Duration:	2 weeks
Foreseen dates for the beginning and conclusion:	08/06/2015– 26/06/2015
Institutions, Departments and Services:	CHP – HSA – DM: SD, SG and UIC
Objectives:	Preparation for the JIIC.
Description:	Preparation of the presentation of the project for the JIIC.
Involved investigators:	Rui Pereira
Investigators functions and responsibilities:	Rui Pereira is responsible for the presentation of the project with the help of Dr. Margarida Lima.

Task 8: Oral presentation of the results	
Duration:	2 weeks
Foreseen dates for the beginning and conclusion:	06/06/2016– 24/06/2016
Institutions, Departments and Services:	CHP – HSA – DM: SD, SG and UIC
Objectives:	Preparation for the JIIC.
Description:	Preparation of the presentation of the results for the JIIC.
Involved investigators:	Rui Pereira
Investigators functions and responsibilities:	Rui Pereira is responsible for the presentation of the results with the help of Dr. Margarida Lima.

Material and methods

Data recovery instruments

For this project a formulary, present in the addendum list, was created for clinical data recovery.

Data analysis

The data will be analyzed with descriptive statistics to present the characteristics of the population as well as the incidence of adverse events and the groups with higher risk. With statistical inference we will compare the results of our study with previously published studies accounting for the sociodemographic and clinical characteristics of the studied populations.

Scheduling

Date of beginning and conclusion (duration in months)

Global: September of 2014 until July of 2016 (22 months)

Planning: September of 2014 until July of 2015 (11 months)

Execution: September of 2014 until July of 2016 (11 months)

Chronogram

	ACADEMIC YEAR 2014/2015												ACADEMIC YEAR 2015/2016										
Month	09	10	11	12	01	02	03	04	05	06	07	08	09	10	11	12	01	02	03	04	05	06	07
Area selection	x																						
Team integration		x																					
Theme and subject selection		x																					
Problems identification			x																				
Question formulation			x																				
Setting of the Goals			x																				
Bibliographic Review			x																				
Project conception			x																				
Proposal redaction			x	x	x																		
Proposal submission								x															
Proposal presentation										x													
Project execution										x	x		x	x	x								
Results analysis															x	x							
Results presentation																						x	
MIM Thesis presentation																						x	

Production indicators

Oral communications and posters

- Oral presentation of the project proposal in the JIIC (June 2015)
- Oral presentation of the results in the JIIC (June 2016)

Written projects

- Academic research project proposal (February 2015)
- Review article for publication in a national or international medical magazine with scientific arbitration (2015)
- Original article for publication in a national or international medical magazine with scientific arbitration (2015)
- MIM Thesis (July 2016)

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malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials," *Jama*, vol. 295, no. 19, pp. 2275–2285, 2006.
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Other questions with ethical implications

Privacy and anonymization

A data crossing key will be implemented to keep apart the data from the patient's identification.

Other aspects

In regard to standing CHP regulation the data from clinical processes will be consulted under supervision of the tutor in a suitable place inside CHP installations.

Budget

	Estimated costs (€)
Administrative material (printing, paper, etc.)	*00,00
Publication costs for a review article and an article presenting the results	750,00
Poster printing for presentation of the results	*00,00
Jornadas de Iniciação à Investigação Clínica (JIIC) Organization	50,00
TOTAL	**800,00**

*Printing available through ICBAS/UP

Funding

This project will be funded by ICBAS/UP, through a grant reserved for DIIC.

Abbreviations

IMID, Immune-mediated inflammatory diseases
TNF, Tumor necrosis factor
Ps, Psoriasis
PsA, Psoriatic arthritis
RA, Rheumatoid arthritis
AS, Ankylosing spondylitis
CD, Crohn's disease
UC, Ulcerative colitis

Acronyms

CHP, Centro Hospitalar do Porto
DIIC, Disciplina de Iniciação à Investigação Clínica.
DM, Departamento de Medicina.
HSA, Hospital de Santo António.
SD, Serviço de Dermatologia
SG, Serviço de Gastrenterologia
UIC, Unidade de Imunologia Clínica
ICBAS, Instituto de Ciências Biomédicas Abel Salazar.
JIIC, Jornadas de Iniciação à Investigação Clínica.
MIM, Mestrado Integrado em Medicina.
UP, Universidade do Porto.

Addendum list

- Formulário de recolha de dados
- Lista de documentos para trabalhos académicos de investigação (que conferem grau)
- Folha de rosto do estudo de investigação
- Pedidos de autorização (Presidente do Conselho de Administração do CHP, Presidente da Comissão de Ética para a Saúde do CHP, Diretora do Departamento de Ensino, Formação e Investigação do CHP).
- Termos de responsabilidade (Aluno, Orientador, Regente da DIIC)
- Autorizações locais (Departamentos e Serviços do CHP envolvidos no projeto)
- Carta dirigida ao Presidente da Comissão de Ética para a Saúde do CHP a solicitar dispensa de consentimento informado

Formulário de recolha de dados

Trabalho académico de investigação:

Safety of anti-TNF therapies in immune-mediated inflammatory diseases: focus on infections and malignancy

Aluno da DIIC do curso de MIM do ICBAS/UP e do CHP:

Rui Pereira

INFORMAÇÃO GERAL

Género M □ F □ **Data de Nascimento** _____ /_____ /_____

Antecedentes HBV □ HCV □ HIV □ Tuberculose □ Neoplasias □ Outros □

Quais

_____

Rastreio tuberculose Mantoux □ + □ - □ Rx □ + □ - □ IGRA □ + □ - □

Quimioprofilaxia

_____

Comorbilidades

Quais _____

Tabagismo S □ N □ **Álcool** S □ N □

INFORMAÇÃO DA DOENÇA

Doença Artrite Reumatoide □ Espondilite anquilosante □

Espondiloartropatia não radiológica □ Artrite idiopática juvenil □

IBDU □ Doença de Crohn □ Colite Ulcerosa □ Psoriase □ Artrite Psoriática □

Data de diagnóstico _____ /_____ /_____

TERAPÊUTICA

Infliximab □ Adalimumab □ Etanercept □ Certolizumab □ Golimumab □

Data (início) _____ /_____ /_____ Data (fim) _____ /_____ /_____

Dose média _____

Frequência _____

Razão da suspensão

_____

Monoterapia □ Terapêutica adjuvante □

Imunomoduladores □

Quais _____

Data (início) _____ /_____ /_____ Data (fim) _____ /_____ /_____

Razão da suspensão _____ Dose média _____

Corticóides Sistémicos □ Quais _____

Data (início) _____ /_____ /_____ Data (fim) _____ /_____ /_____

Razão da suspensão _____ Dose média _____

INTERCORRÊNCIAS

Vacinação Influenza □ Pneumocócica □

Outras _____

Rastreio anual TB □ Mantoux □ + □ - □ Rx □ + □ - □ IGRA □ + □ - □

Intervenções cirúrgicas Quais (datas)

_____

_____

Complicações

Infecção □ Infecção Severa □ Neoplasias □

Outras _____

Data _____ /_____ /_____

Órgão _____

Agente causal

_____

Consequências Int transitória □ Int definitiva □ Switch do anti-TNF □ Morte □

Outras _____

Lista de documentos para

TRABALHOS ACADÉMICOS DE INVESTIGAÇÃO (que conferem grau)

	Data de entrega (ou NA, não aplicável)	Secretariado (Assinatura)
Documentos comprovativos		
Inscrição em Licenciatura, Mestrado ou Doutoramento	NA	
Cartas do Aluno, a solicitar autorização institucional		
Presidente do Conselho de Administração	X	
Presidente da CES	X	
Diretor do DEFI	X	
Termos de responsabilidade de Alunos e Orientadores		
Aluno	X	
Orientador do Projeto	X	
Supervisor do Projeto, Docente responsável pela DIIC	X	
Termos de autorização local (no CHP)		
Responsáveis por Unidades / Gabinetes / Setores*	NA	
Diretores de Serviço	X	
Diretores / Conselhos de Gestão de Departamentos	X	
Proposta		
Folha de Rosto do Estudo de Investigação (modelo próprio)	X	
Proposta de Trabalho Académico de Investigação	X	
Anexos		
Curriculum Vitae do Aluno	NA	
Termo de Consentimento Informado	NA	
Folheto com informação para dar aos Participantes	NA	
Carta a solicitar dispensa de Consentimento Informado*	X	
Inquéritos / questionários ou guiões de entrevistas*	NA	
Formulário para recolha de dados dos processos clínicos*	X	
Outros documentos*	NA	

*** Se aplicável.**

SECRETARIADO: Data de conclusão da entrega de documentação

Data Assinatura

___/___/_____ _____

Folha de rosto do estudo de investigação

TÍTULO

SAFETY OF ANTI-TNF THERAPIES IN IMMUNE-MEDIATED INFLAMMATORY DISEASES: FOCUS ON INFECTIONS AND MALIGNANCY

CLASSIFICAÇÃO

Trabalho Académico de Investigação ☑ (Mestrado Integrado em Medicina)
Projecto de Investigação ☑
Ensaio Clínico □ Medicamentos □ Dispositivos médicos □
Outro □ Qual?

VERSÃO

Novo ☑ Modificação / Adenda□ Prolongamento □

CALENDARIZAÇÃO

Data início: Maio 2015 Data conclusão: Junho 2016 Prazo a cumprir: Junho 2016

ALUNOS E ORIENTADORES

Aluno

Rui Pereira, ICBAS/UP, 5º ano do MIM, ppereira.rui@gmail.com, 916370627

Orientador do projeto

Tiago Torres, médico, especialista em Dermatologia e Venereologia assistente hospitalar, Serviço de Dermatologia do CHP; Doutorado em Ciências Médicas, ICBAS/UP, tiagotorres2002@hotmail.com

Supervisor do projeto / Responsável pela DIIC

Margarida Lima, médica, especialista em Imunohemoterapia assistente hospitalar graduada, consultora, Serviço de Hematologia Clínica do CHP; Doutorada em Ciências Médicas, ICBAS/UP, margaridalima@chporto.min-saude.pt

OUTROS INVESTIGADORES

Investigadores

Paula Lago, especialista em Gastrenterologia assistente hospitalar graduada, Serviço de Gastrenterologia do CHP
Raquel Faria, especialista em Medicina Interna, assistente hospitalar, Serviço de Medicina do CHP;

PROMOTOR O próprio ☑

INSTITUIÇÕES E SERVIÇOS

Unidades, Departamentos e Serviço do CHP

Departamento de Medicina: Serviço de Dermatologia (Proponente), Serviço de Gastrenterologia e Unidade de Imunologia Clínica

Outras Instituições intervenientes

CARATERÍSTICAS do estudo (Assinale as opções corretas)

Alvo do estudo

Animais □ Humanos ☑

Multicêntrico □ Institucional ☑

Países / Instituições envolvidos

Multinacional □ Nacional ☑

Natureza do estudo

Clínico ☑ Terapêutico ☑

Epidemiológico □ Laboratorial □

Caraterísticas do estudo (desenho)

Descritivo ☑ Analítico ☑

Observacional ☑ Experimental □

Transversal ☑ Longitudinal □

(Retrospetivo ☑ Prospetivo □)

Estudo de síntese □ (Revisão narrativa □ Revisão sistemática □ Revisão sistemática meta-análise □)

Participantes

Existência de grupo controlo: Não ☑ Sim □

Seleção dos Participantes: Aleatória □ Não aleatória ☑

Estudos observacionais:

Tipo: Caso □ Série de casos ☑ Casos-controlos □ Coortes □ Outro □

Estudos experimentais:

Conhecimento: Aberto □ Cego □ (Duplamente cego □)

Ensaios Clínicos: Fase I □ Fase II □ Fase III □ Fase IV □

Outros aspetos relevantes para a apreciação do estudo:

Participação de grupos vulneráveis Não ☑ Sim □

Convocação de doentes / participantes Não ☑ Sim □

Consentimento informado Não ☑ Sim □ (Carta a solicitar dispensa: Não □ Sim ☑)

Inquéritos / questionários Não ☑ Sim □

Entrevistas Não ☑ Sim □

Colheita de produtos biológicos Não ☑ Sim □

Armazenamento de produtos biológicos Não ☑ Sim □

Criação de bancos de produtos biológicos Não ☑ Sim □

Realização de exames / análises Não ☑ Sim □

Realização de estudos genéticos Não ☑ Sim □

Recolha de dados Não □ Sim ☑ (Dados: clínicos ☑ laboratoriais: analíticos ☑ / imagem ☑)

Criação de bases de dados Não □ Sim ☑ (Não anonimizadas □ Anonimizadas ☑) - Ficheiro de Excel

Saída para outras instituições Não ☑ Sim □

ORÇAMENTO E FINANCIAMENTO

Orçamento total: 800 Euros Contrato financeiro em anexo: Não ☑ Sim □

Financiamento: Interno (CHP): 0 Euros Externo (Outros): 800 Euros

Entidades financiadoras: Bolsa do ICBAS para os alunos da DIIC

INDICADORES

Dissertação MIM ☑

Data: Abril 2015 Assinatura do proponente (Aluno):

Pedidos de autorização institucional

Trabalho académico de investigação:

Safety of anti-TNF therapies in immune-mediated inflammatory diseases: focus on infections and malignancy

Aluno da DIIC do curso de MIM do ICBAS/UP e do CHP:

Rui Pereira

Presidente do Conselho de Administração do CHP

Exmo. Senhor Presidente do Conselho de Administração do CHP

Rui Miguel Pedrosa Pereira, na qualidade de Aluno, vem por este meio, solicitar a Vossa Exa. autorização para realizar no Centro Hospitalar do Porto o Estudo de Investigação acima mencionado, de acordo com o programa de trabalhos e os meios apresentados.

Data Assinatura

___/___/_____ _____

Presidente da Comissão de Ética para a Saúde do CHP

Exma. Senhora Presidente da Comissão de Ética para a Saúde do CHP

Rui Miguel Pedrosa Pereira, na qualidade de Aluno, vem por este meio, solicitar a Vossa Exa. autorização para realizar no Centro Hospitalar do Porto o Estudo de Investigação acima mencionado, de acordo com o programa de trabalhos e os meios apresentados.

Data Assinatura

___/___/_____ _____

Diretora do Departamento de Ensino, Formação e Investigação do CHP

Exma. Senhora Diretora do Departamento de Ensino, Formação e Investigação do CHP

Rui Miguel Pedrosa Pereira, na qualidade de Aluno, vem por este meio, solicitar a Vossa Exa. autorização para realizar no Centro Hospitalar do Porto o Estudo de Investigação acima mencionado, de acordo com o programa de trabalhos e os meios apresentados.

Data Assinatura

___/___/_____ _____

Termos de responsabilidade

Trabalho académico de investigação:

Safety of anti-TNF therapies in immune-mediated inflammatory diseases: focus on infections and malignancy

Aluno da DIIC do curso de MIM do ICBAS/UP e do CHP:

Rui Pereira

Aluno

Na qualidade de Aluno, comprometo-me a executar o estudo de investigação acima mencionado, de acordo com o programa de trabalhos e os meios apresentados, respeitando os princípios éticos e deontológicos e as normas internas da instituição.

Aluno	Data	Assinatura
Rui Pereira	___/___/___	

Orientador do projeto

Na qualidade de Orientador, solicito autorização do Conselho de Administração para que o Aluno acima referido possa desenvolver no CHP o seu estudo de investigação. Informo que me comprometo a prestar a orientação necessária para uma boa execução do mesmo e a acompanhar o Aluno nas diferentes fases da sua realização, de acordo com o programa de trabalhos e meios apresentados, bem como por zelar pelo respeito dos princípios éticos e deontológicos e pelo cumprimento das normas internas da instituição.

Nome	Data	Assinatura
Tiago Torres	___/___/___	

Instituição	Departamento	Serviço / Setor
CHP	Medicina	Dermatologia

Supervisor do projeto / Responsável pela DIIC

Na qualidade de Docente Responsável pela DIIC / Supervisor do Aluno no CHP, comprometo-me a prestar a orientação necessária para uma boa execução do estudo de investigação, de acordo com o programa de trabalhos e meios apresentados. Mais declaro que acompanharei o Aluno, responsabilizando-me por supervisionar a execução do trabalho no CHP, bem como por zelar pelo respeito dos princípios éticos e deontológicos e pelo cumprimento das normas internas da instituição.

Nome	Data	Assinatura
Margarida Lima	___/___/___	

Docente responsável pela DIIC

Termos de autorização local

Estudo de investigação:

Safety of anti-TNF therapies in immune-mediated inflammatory diseases: focus on infections and malignancy

Aluno da DIIC do curso de MIM do ICBAS/UP e do CHP:

Rui Pereira

Diretores de Serviço

Na qualidade de Diretor de Serviço, declaro que autorizo a execução do estudo de investigação acima mencionado e comprometo-me a prestar as condições necessárias para a boa execução do mesmo, de acordo com o programa de trabalhos e os meios apresentados.

Serviço	Nome do Diretor	Data	Assinatura
Dermatologia	Manuela Selores	___/___/___	
Gastrenterologia	Isabel Pedroto	___/___/___	
Unidade de Imunologia Clínica	Carlos Vasconcelos	___/___/___	

Diretores / Conselhos de Gestão de Departamento

Na qualidade de Diretor do Departamento, declaro que autorizo a execução do estudo de investigação acima mencionado e comprometo-me a prestar as condições necessárias para a boa execução do mesmo, de acordo com o programa de trabalhos e os meios apresentados.

Departamento	Nome do Diretor	Data	Assinatura
Medicina	Rui Sarmento	___/___/___	

Carta dirigida ao Presidente da Comissão de Ética para a Saúde do CHP a solicitar dispensa de consentimento informado

Estudo de investigação:

Safety of anti-TNF therapies in immune-mediated inflammatory diseases: focus on infections and malignancy

Aluno da DIIC do curso de MIM do ICBAS/UP e do CHP:

Rui Pereira

Exma. Senhora Presidente da Comissão de Ética para a Saúde do CHP

Rui Miguel Pedrosa Pereira, na qualidade de Aluno, vem por este meio, solicitar a Vossa Exa. dispensa do consentimento informado na realização do Estudo de Investigação acima mencionado visto este ser de carácter retrospetivo. No âmbito do mesmo o registo dos dados clínicos dos doentes (evidenciados em formulário em anexo) será feito com supervisão direta do tutor nas instalações do Serviço de Dermatologia do CHP e será anonimizado garantindo a confidencialidade dos dados.

Data

___/___/_____

Assinatura

_____

ANEXOS

Documentos do projeto de investigação

centro hospitalar do Porto

Hospital Santo António | Hospital Maria Pia | Maternidade Júlio Dinis | Hospital Joaquim Urbano

Largo Prof. Abel Salazar
4099-001 PORTO
www.hgsa.pt

Exmo. Sr.

Rui Pereira

Aluno do ICBAS

ASSUNTO: Projeto de Investigação Trabalho Académico PI/DIIC/MIM - **"Safety of anti-TNF therapies in immune-mediated inflammatory diseases: focus on infections and malignancy" - N/ REF.ª 2015.120(107-DEFI/100-CES)**

O Conselho de Administração do CHP **autoriza** a realização do estudo de investigação acima mencionado nesta Instituição, nos Serviços de Dermatologia, Gastrenterologia e Unidade de Imunologia Clínica, sendo Investigador Principal, o aluno do ICBAS, Rui Pereira.

O estudo de investigação foi previamente analisado pela Comissão de Ética para a Saúde e Gabinete Coordenador de Investigação do Departamento de Ensino, Formação e Investigação do CHP, bem como pela Direção Clínica, tendo obtido Parecer Favorável.

Cumprimentos,

CONSELHO DE ADMINISTRAÇÃO
21/6/2015
Dr. SOLLARI ALLEGRO — Presidente
Dr.ª ÉLIA GOMES — Vogal Executiva
Dr. PAULO BARBOSA — Director Clínico
Dr. RUI PEDROSO — Vogal Executivo
Enf.º EDUARDO ALVES — Enfermeiro Director

* Em todas as eventuais comunicações posteriores sobre este estudo é indispensável indicar a nossa ref.ª.

centro hospitalar do Porto

Hospital de Santo António Maternidade Júlio Dinis Hospital Maria Pia

Largo Professor Abel Salazar
4099 - 001 PORTO
www.hgsa.pt

APRECIAÇÃO E PARECER PARA A REALIZAÇÃO DE **PI/DIIC/MIM**

Título: **"Safety of anti-TNF therapies in immune-mediated inflammatory diseases: focus on infections and malignancy"**		Ref.ª: **2015.120(107-DEFI/100-CES)**
Protocolo/Versão:		Investigador: **Rui Pereira** **Aluno do ICBAS**

DIRECÇÃO DE ENFERMAGEM:	**DIRECÇÃO CLÍNICA:**
☒ **NÃO SE APLICA**	☒ **PARECER FAVORÁVEL**
☐ **PARECER FAVORÁVEL**	☐ **PARECER NÃO FAVORÁVEL**
☐ **PARECER NÃO FAVORÁVEL**	
Data:	Data:
_____	**Dr. PAULO BARBOSA** Diretor Clínico - CHP Data: 23/6/2015

Em conformidade. Pode ser autorizado

Prof.ª Doutora Luísa Lobato
Diretora do DEFI

Prof.ª Doutora Luísa Lobato
Diretora do DEFI

16/06/2015

centro hospitalar
do Porto

Hospital de Santo António Maternidade Júlio Dinis Hospital Maria Pia

Largo Professor Abel Salazar
4099 - 001 PORTO
www.hgsa.pt

COMISSÃO DE ÉTICA PARA A SAÚDE

APRECIAÇÃO E VOTAÇÃO DO PARECER

Deliberação	Data: 3.6.2015	Órgão: Reunião Plenária

Título: **"Safety of anti-TNF therapies in immune-mediated inflammatory diseases: focus on infections and malignancy"**		Ref.ª: **2015.120(107-DEFI/100-CES)**
Protocolo/Versão: **TRABALHO ACADÉMICO - MIM**	Promotor: **o(a) próprio(a)**	Investigador: **Rui Pereira ICBAS**

A Comissão de Ética para a Saúde – CES do CHP, ao abrigo do disposto no Decreto-Lei n.º 97/95, de 10 de Maio, em reunião realizada nesta data, apreciou a fundamentação do relator sobre o pedido de parecer para a realização de **TRABALHO ACADÉMICO - MIM** acima referenciado:

Ouvido o Relator, o processo foi votado pelos Membros da CES presentes:

Presidente: Dr.ª Luisa Bernardo

Dr.ª Paulina Aguiar, Dr.ª Fernanda Manuela, Enf.ª Paula Duarte, Prof.ª Carla Teixeira, Prof.ª Doutora Maria Manuel Araújo Jorge, Dr. Jorge Andrade da Silva

Resultado da votação:

PARECER FAVORÁVEL

A deliberação foi aprovada por unanimidade.

Pelo que se submete à consideração superior.

AUTORIZADO
Dr. Severo Torres
Adjunto do Diretor Clínico
Data: 23/6/2015

Data 3.6.2015

A Presidente da CES

Dr.ª Luisa Bernardo